Depression in Epilepsy

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Depression in Epilepsy

by

Kirsten Marie Fiest

A THESIS
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Abstract

A relationship between depression and epilepsy has been consistently reported in the literature. Most of this research has estimated the proportion of people with depression in epilepsy. More recently, research has focused on determining fast and accurate methods of diagnosing depression in clinical samples. In contrast, there is a relative dearth of research into the treatment of depression in epilepsy using both pharmacological and non-pharmacological methods. Despite this research, there are still gaps in the knowledge base of this association. The literature on depression in epilepsy has not been reviewed and summarized. Screening tools for identifying depression in epilepsy have either not been validated, or have not been validated with a gold standard tool. Finally, patterns of pharmacological and non-pharmacological treatment of depression in epilepsy have not been well characterized. The work reported in this dissertation addresses each of these three knowledge gaps. Based on a systematic review, the overall pooled prevalence of active depression in persons with epilepsy was found to be 23.1% (95% Confidence Interval: 20.6%-28.3%), and the overall odds ratio of active depression in those with epilepsy, relative to those without, was 2.77 (95% CI: 2.09-3.67). Three depression screening tools, one of which was previously not validated, and new cut-points for scoring were explored in a group of 185 persons with epilepsy. Compared to a gold-standard diagnostic interview, the tools with the best overall balance of sensitivity and specificity were the Hospital Anxiety and Depression Scale at a cut-point of seven and the Patient Health Questionnaire with a cut-point of nine. Newly suggested cut-points for scoring performed better than those cut-points recommended for use in the general population. Considering both pharmacological and non-pharmacological treatments for depression in persons with epilepsy, the majority of persons (70.3%) with current depression were not receiving depression-related therapy. Of those treated,
most were receiving non-pharmacological treatments for depression. More persons with a past history of depression (37.2%) were receiving treatment, of which the majority was by pharmacological management. The results of these studies characterize the identification and management of depression, addressing knowledge gaps and providing direction for future research.
Preface

For this thesis, the following three manuscripts have been published, or have been submitted for publication. For each of the manuscripts, the first author conducted the analyses, interpreted the results and wrote the manuscripts. All three studies were completed under the guidance of the senior authors and supervisors. All authors critically revised the manuscripts and contributed intellectually to each work. The manuscripts are reproduced in their entirety as chapters in this thesis, after written permission was obtained from the publishers and co-authors.


Acknowledgements

I would like to thank everyone who supported me through this journey. To my supervisors, Dr. Scott Patten and Dr. Nathalie Jetté, thank you for your support, encouragement and guidance. I have learned so much from both of you. To my thesis committee members, your wisdom, feedback and mentorship are greatly appreciated. A very special thanks to Alex Frolkis- I could not have made it through this without you. Since day one of this program you have provided me with endless support, confidence and laughs. We did it! To Khara and Jodie, my lab mates and friends, you truly made this a wonderful experience. We have travelled far and wide, always supporting each other through the highs and lows- thank you. My parents have never stopped supporting my dreams, thank you for always being there for me, no matter what. You really make me feel that I can do anything. And finally to Matthew, without your patience and understanding I could not have done this. Thank you for always bringing things into perspective, and for believing in me.
Dedication

To my parents, my grandparents and my love.
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<tr>
<td>AED</td>
<td>Antiepileptic Drug</td>
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<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
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<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DBS</td>
<td>Deep Brain Stimulation</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual for Mental Disorders</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GABA</td>
<td>Gamma Aminobutyric Acid</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal</td>
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<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>MDI</td>
<td>Major Depression Inventory</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MOOSE</td>
<td>Meta-Analysis of Observational Studies in Epidemiology</td>
</tr>
<tr>
<td>NDDI-E</td>
<td>Neurological Disease and Depression Inventory-Epilepsy</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PEARLS</td>
<td>Program to Encourage Active, Rewarding Lives for Seniors</td>
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<tr>
<td>PHQ</td>
<td>Patient Health Questionnaire</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>PWE</td>
<td>Person with Epilepsy</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV</td>
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<tr>
<td>Se</td>
<td>Sensitivity</td>
</tr>
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<td>Sp</td>
<td>Specificity</td>
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<tr>
<td>SF-12</td>
<td>Short Form-12</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin-Norepinephrine Reuptake Inhibitor</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>UPLIFT</td>
<td>Using Practice and Learning to Increase Favourable Thoughts</td>
</tr>
<tr>
<td>VNS</td>
<td>Vagus Nerve Stimulation</td>
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CHAPTER 1: INTRODUCTION
1.1 Overview of Research Project

This dissertation investigates the relationship between depression and epilepsy, two common health conditions. In the following document, the literature will be described and three publications will be presented, followed by a discussion of the results and conclusions, and finally considerations for future research. Section 1.2 discusses the overall aim of the dissertation. Section 1.3 provides background information; specifically, section 1.3.1 discusses epilepsy, 1.3.2 depression, and 1.3.3 briefly discusses the association between depression and epilepsy, while section 1.3.4 describes the bi-directional relationship between the two conditions. Section 1.3.5 examines possible psychosocial and neurobiological mechanisms that may explain the observed association between depression and epilepsy. In section 1.3.6 screening for depression is discussed broadly, and in the context of epilepsy. The treatment of depression in epilepsy is discussed in section 1.3.7 and knowledge gaps are addressed in section 1.4. Thesis objectives are described in section 1.5 and a broad outline of the dissertation is detailed in section 1.6.

Sections 2, 3, and 4 are the main body of the dissertation; each representing a journal article that is published or in preparation. These papers are: (1) a systematic review and meta-analysis of the population-based association between depression and epilepsy; (2) a validation of depression screening tools for use in persons with epilepsy; and (3) a description of treatment patterns of depression in epilepsy.

Section 5 is the final chapter, which is a discussion of the relationship between depression and epilepsy broadly, and in light of the studies conducted for this dissertation. Section 5.1 provides a summary of the main study findings. In section 5.2 challenges and limitations in
studying the association between depression and epilepsy are discussed. The clinical and public health implications of this work are described in section 5.3 and directions for future research are explored in the final section, 5.4.

1.2 Aim

The overarching aim of this dissertation was to explore the relationship between depression and epilepsy. In order to quantify and examine factors associated with this relationship, a variety of data and methodologies were employed.

1.3 Background

1.3.1 Epilepsy

Epilepsy is a disorder of the central nervous system, characterized by a predisposition to generate epileptic seizures and subsequent effects on mental, physical or behavioral functioning[1]. In primary practice, epilepsy ranks as the second most commonly reported neurological condition worldwide[2] with a self-reported prevalence of epilepsy in Canada of 5.6 per 1000 persons[3]. Persons with epilepsy access the health care system frequently, and the condition is associated with significant treatment gaps and disparities in care[4, 5]. Epilepsy has a substantial impact on health, including numerous social difficulties, impaired quality of life, perceived and enacted stigma, and lifestyle restrictions[6].

The International League Against Epilepsy (ILAE) commissioned a report, released in 2011, to standardize epidemiologic studies reporting on epilepsy[7]. The report focused on three main areas: (1) conceptual and operational definitions of epilepsy; (2) data resources and data elements; and (3) appropriate methods and analyses[7]. Common definitions of epilepsy are essential for research to be compared across studies and time; the authors propose both a conceptual and operational definition of epilepsy[7]. The conceptual definition, most useful for
clinicians diagnosing epilepsy, is “a disorder characterized by an enduring predisposition to
generate epileptic seizures and by neurobiologic, cognitive, psychological and social
consequences of this condition”[7]. The definition requires the occurrence of at least one
epileptic seizure[7]. The operational definition is most useful in epidemiologic studies: “two or
more unprovoked seizures occurring at least 24 hours apart”[7]. The authors propose using the
classification of seizure types and etiology proposed in the revised 2010 ILAE report (see
below)[8]. Estimates of prevalence and incidence are suggested as outcome measures, along with
absolute and relative measures of association[7]. It is suggested that comorbidities, access to
care, disparities in care, quality of life and burden be assessed in future studies focused on
persons with epilepsy[7].

Publications by the ILAE Commission on Classification and Terminology have shaped
how the etiology of epilepsy and the classification of seizure types are defined[8, 9]. The 2010
epilepsy and seizure classification system reflects advances in basic and clinical
neurosciences[8]. Focal and generalized seizures are defined as occurring within networks
limited to one hemisphere or in rapidly engaging, bilaterally distributed networks,
respectively[8]. Focal seizures are described according to the degree of impairment during a
seizure, broadly, they are: without impairment of consciousness or awareness (with observable
motor or autonomic components or involving subjective sensory or psychic phenomena), with
impairment of consciousness or awareness (“dyscognitive features”), and evolving to a bilateral,
convulsive seizure[8]. The types of generalized seizures are: (1) tonic-clonic seizures; (2) clonic
seizures; (3) tonic seizures; (4) atonic seizures; (5) myoclonic seizures (and its subtypes); and (6)
absence seizures (and its subtypes)[8]. Rigorous classification systems such as this allow for
uniformity and consistency in the reporting of seizures and epilepsies.
The ILAE divides the etiology of epilepsy into three distinct groups: (1) genetic; (2) structural/metabolic; and (3) unknown[8]. Genetic epilepsies are “the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder”[8]. Structural/metabolic epilepsies are the result of another structural or metabolic condition, including acquired disorders and genetic conditions, in which there is a separate condition between the genetic defect and the epilepsy[8]. Epilepsy of an unknown etiology is a category for those epilepsies where the cause is not currently known, but may be of genetic origin or the result of a separate, unrecognized disorder[8]. Several genes and mutations have been implicated in the pathogenesis of epilepsy; these include the $GABA_1$ and $EFHC1$ genes in the development of juvenile myoclonic epilepsy and the $CACNA1A$ and $ECA1$ loci in the development of absence epilepsy[10]. Brain injury is a common risk factor for structural/metabolic epilepsy, leading to 6% of all epilepsies in a population-based study of over two million Americans[11]. The greatest risk factor for epilepsy in this population was cerebrovascular disease, which accounted for 11% of the cases of epilepsy[11]. Neurocysticercosis, a parasitic disease of the nervous system, is one of the most common causes of epilepsy in endemic areas, such as Latin America and Africa[12-14].

1.3.2 Depression

A major depressive episode is characterized by depressed mood or markedly diminished interest in almost all activities, accompanied by additional specified physical or psychological symptoms[15]. Common features of a major depressive episode include fatigue, appetite changes, sleep changes, psychomotor agitation or retardation (restlessness or moving more slowly than normal), difficulties with concentration, feelings of worthlessness or guilt, and suicidal thoughts, plans or attempts[15]. According to the Diagnostic and Statistical Manual-5
(DSM-5), to be considered a major depressive episode, symptoms must persist for up to two weeks and cause marked distress or interfere with social, occupational or educational functioning[15]. The DSM-5 is the most recent version of the DSM criteria- the only change in the diagnostic criteria of depression from the DSM-IV-TR is the removal of the bereavement exclusion[15]. The symptoms of depression must not be due to the effects of a general medical condition or the effects of a substance[15]. Major depressive disorder can be characterized by a single major depressive episode or recurrent depressive episodes[15]. A major depressive episode can be distinguished from depressive symptoms, which alone do not indicate clinical depression[16]. Self-report rating scales assess depressive symptoms rather than a diagnosis of major depression. The term depression will be used to describe one or more major depressive episodes (major depressive disorder) in the absence of any manic, hypomanic or mixed episodes (which would indicate a bipolar disorder), and depressive symptoms will be used to describe those characteristics that may indicate depression, but on their own are not sufficient for diagnosis.

Globally, depression is the second leading cause of years of life lived with disability, and the eleventh leading cause of disability-adjusted life-years, which accounts for premature mortality[17, 18]. The 12-month prevalence of depression is 4.7%[19], with a lifetime prevalence of up to 16.6% in adults over 18 years[20]. Depression is associated with a number of direct and indirect costs, such as outpatient & pharmaceutical costs and productivity loss[21]. It is estimated that neuropsychiatric conditions will account for 14.7% of the total global burden of disease by 2020[2].

The underlying biological mechanisms and etiology related to depression are not clearly understood, though numerous theories have been suggested. A recent study by Patten[22]
assessed the interaction of childhood adverse events and adult stressors to demonstrate a greater than additive relationship in the risk of developing a future major depressive episode. Longitudinal data from the Canadian National Population Health Survey show that indeed there is a synergistic (greater than additive) relationship between childhood adverse events and adult stressors[22]. This indicates that the interaction of both childhood adverse events and adult stressors has a greater impact on the development of a future depressive episode than either alone, implying that these risk factors participate together in shared causal mechanisms[22]. These findings support previously posited theories on the concept of depression etiology, such as the diathesis-stress model, which states that an initial vulnerability, or diathesis (potentially caused by childhood adverse events or negative cognitive schemas), is latent until a stressor (significant stress in adulthood or a genetic predisposition) activates a maladaptive response.

The neurobiology of depression has been the focus of a great amount of research, specifically investigating dysregulation of both the hypothalamic-pituitary-adrenal (HPA) axis and the hippocampus[85, 86]. Implicated in this dysregulation are corticotropin-releasing factor, glucocorticoids and brain-derived neurotrophic factor (BDNF) [85, 86]. The neurotrophic hypothesis of depression states that the hippocampal dysfunction occurring during the development of depression is partially due to a deficiency in neurotrophic support in the brain[85]. BDNF is one of the most common neurotrophic factors; acute and chronic stress reduce levels of BDNF in the brain, however the administration of antidepressants increases BDNF expression in affected areas[85]. Research into specific linkages and mechanisms between BDNF and the hippocampus are limited, though promising avenues of future research.

Dysregulation of monoamine neurotransmitter systems (eg. dopamine, serotonin, norepinephrine) is another suggested mechanism for the etiology of depression[23]. Lifestyle
factors, such as increased alcohol consumption, smoking and decreased physical activity are proposed to affect the development of depression[24]. Other factors, such as female sex[25], a previous depressive episode[26] and genetic heritability[23] are also related to the development of depression.

1.3.3 Association between Epilepsy & Depression

Epilepsy is associated with an increased risk of psychiatric comorbidities, such as anxiety and depression[27, 28]. In recent years mounting research has focused on the association between epilepsy and depression. Depression is often under-recognized and improperly managed in persons with epilepsy, and can interfere with treatment outcomes and quality of life in this population[29]. Under-managed depression in epilepsy may also lead to missed work, increased health-care system utilization, and higher direct medical costs[30, 31]. Although an association between epilepsy and depression has been described, the literature is inconsistent. Recent estimates report the prevalence of depression (either current or lifetime) in epilepsy in the general population to be 12-37%, reaching as high as 55% in clinical samples[32, 33]. The range of these estimates is striking, and it is unclear which factors may contribute to these heterogeneous findings. It is possible that the study population, data source, or method of diagnosing both depression and epilepsy could be responsible for these disparate estimates of prevalence.

1.3.4 Bi-directional Relationship between Depression and Epilepsy

A bi-directional relationship between depression and epilepsy has been reported in the literature; epilepsy is considered a risk factor for depression and depression may increase the likelihood of developing epilepsy[34-36]. A recent matched, longitudinal cohort of over 17,000 individuals from the United Kingdom’s General Practice Research Database showed
significantly increased incidence rate ratios (ranging from ~1.5-3.0) for depression in the three years before and after the onset of epilepsy[36]. This bi-directional relationship does not in itself indicate a causal relationship, but more likely represents a shared biological mechanism[37]. Many such mechanisms have been proposed, including: (1) abnormal activity or sensitivity in serotonin, norepinephrine, dopamine or glutamate neurotransmitters; (2) structural changes to temporal or frontal lobe structures; (3) abnormal functioning of the hypothalamic-pituitary-adrenal axis; and (4) functional changes to temporal or frontal lobe structures [37-39]. Pathogenesis in these shared neurological pathways may promote the development of one condition when the other is also present[38]. Understanding the etiology of depression in epilepsy is important, as there are implications for quality of life, seizure control and other health outcomes[38].

1.3.5 Possible Explanatory Mechanisms

Numerous psychological, social and neurobiological mechanisms have been proposed to explain the relationship between depression and epilepsy. It is likely that no mechanism operates on its own, but rather a combination of factors may influence the relationship between depression and epilepsy. The predisposing, precipitating and perpetuating factors may differ between individuals, leading to varying disease manifestations and expressions.

1.3.5.1 Psychosocial Factors

Initially, depression was believed to be an inevitable consequence of having epilepsy, the result of psychosocial stress and unpredictability[40, 41]. Proposed by Seligman in the 1960s, learned helplessness is a paradigm that remains one of the most prominent behavioral models of depression[42]. In learned helplessness, people are conditioned to believe that an aversive situation is unavoidable or inescapable[42]. For persons with epilepsy, the unpredictable and
uncontrollable nature of seizures may lead to a situation of learned helplessness, where a lack of feeling of personal control exists[42].

The diathesis-stress model of depression explains why some people develop depression in response to stressful life events, while others remain resilient and do not[42]. This model states that depression is the result of an interaction between life events (stress) and a biological predisposition (diathesis); this determines the extent to which the body reacts during challenging and threatening situations[42]. In the case of epilepsy, a state of chronically increased stress leads to the development of depression more often than in people without epilepsy[42].

Depressive disorders have a significant impact on quality of life in persons with epilepsy. Depression - not seizure frequency - is the greatest independent predictor of quality of life in persons with epilepsy[43]. The presence of other social factors, such as the ability to work, drive and maintain a stable family life have been found to reduce the risk of developing depression in epilepsy[42]. Persons with chronic illnesses commonly experience stigma, and this may be even more pronounced in persons with epilepsy[44]. Persons with epilepsy are often perceived as scary, out of control or aggressive[44]. Stigmatized persons with epilepsy experience decreased quality of life compared to those persons with epilepsy who do not experience stigma[44].

1.3.5.2 Neurobiological Factors

In epilepsy, depression may precede the onset of a seizure (pre-ictal), follow the cessation of a seizure (post-ictal), be present between seizures (inter-ictal) or be the result of medication (iatrogenic)[38]. Four neurobiological mechanisms are commonly cited as the most likely links between depression and epilepsy: (1) abnormal activity/receptor sensitivity of several neurotransmitters; (2) structural changes in temporal and frontal lobe structures; (3) functional abnormalities in the temporal and frontal lobes; and (4) abnormal function of the HPA axis[37-
Each of these mechanisms plays a role in describing the pathophysiology and development of depression in epilepsy (and vice-versa).

1.3.5.2.1 Abnormal Neurotransmitter Function

Evidence suggests that the neurotransmitters serotonin, norepinephrine, glutamate and γ-aminobutyric acid (GABA) operate in the pathogenesis of both epilepsy and depression[46]. In animal models of epilepsy, genetically prone epilepsy rats have innate deficits in serotonergic and noradrenergic synaptic transmission[46]. A reduction in serotonin or norepinephrine transmission can result in seizure occurrence. Pharmaceuticals that interfere with the release of either neurotransmitter may exacerbate seizures, whereas those that promote their release may reduce seizure frequency[46]. In humans, decreased serotonin transmission in depression may be related to decreased innervation in some brain regions, as evidenced by a decreased density of serotonin neurons in the hippocampus and amygdala of post-mortem brains[46]. Anti-epileptic drugs (AEDs) with established positive psychotropic properties, such as carbamazepine, valproic acid and lamotrigine cause an increase in neuronal serotonin transmission[46]. In a double-blind placebo controlled study of serotonin and norepinephrine transmission in humans, the antidepressant imipramine (with reuptake inhibitory effects) reduced absence and myoclonic seizures[46].

Glutamate is an excitatory neurotransmitter, whereas GABA is inhibitory; dysfunction in both has been implicated in the development of both epilepsy and depression, though the mechanisms have not been fully elucidated[45]. Disturbances in glutamate transporters may be responsible for increased levels of synaptic glutamate, as no other process for the re-uptake of glutamate exists[45]. Increased levels of glutamate in the synapse may lead to excitatory neuronal transmissions (akin to epileptiform discharges) that are higher in amplitude and longer
in duration - a process that may lead to cellular damage[45]. Decreased levels of GABA in pre-frontal and limbic brain regions have been found in persons with depression - though its complex relationship with depression and epilepsy has not been fully established[45].

1.3.5.2.2 Structural Abnormalities

Abnormalities in both temporal and frontal lobe structures have been reported in studies of both depression and epilepsy[37, 41, 46]. The most frequent cause of temporal lobe epilepsy is hippocampal sclerosis (severe neuronal loss and changes to glial cell response in the hippocampus)[37]. In approximately 80% of persons with temporal lobe epilepsy, the site of the epileptogenic focus is the structures of the mesial temporal lobe[37]. The mesial temporal lobe includes the amygdala, hippocampus and parahippocampal gyrus. The prevalence of depression is highest in persons with epilepsy whose seizures evolve from the temporal lobe[37]. The longer depression goes untreated, the greater the deficits seen to the hippocampus; in persons with depression, treatment with an antidepressant may prevent hippocampal degeneration[46]. Atrophy of the amygdala is present in people with depression and in persons with epilepsy with temporal lobe involvement[37]. Though involved in both depression and epilepsy, decreases in structural amygdalar volume are larger in persons with epilepsy than in persons with depression only[46].

Frontal lobe abnormalities are also common in both depression and epilepsy[37, 46]. Persons with depression have smaller frontal lobe volumes than those without depression, and the magnitude of these changes is related to the severity of the depression[37]. Neuropsychological tests of executive (frontal-lobe mediated) functioning show poorer performance in persons with epilepsy and persons with depression relative to that of the general population[46].
1.3.5.2.3 Functional Abnormalities

Functional neuroimaging studies have consistently demonstrated commonalities between persons with depression and persons with epilepsy[37]. Decreased serotonin transmission has been shown in both groups: in persons with depression, serotonin binding increases to normal levels when depression is medically treated and in persons with epilepsy, decreased serotonin binding occurs at the site of the seizure focus[37]. In persons with epilepsy, the reduction in serotonin binding seen in epilepsy alone was extended into areas outside of the epileptic focus in those people with comorbid depression[37].

1.3.5.2.4 Hypothalamic-Pituitary-Adrenal Axis Dysfunction

Less research has focused on how abnormalities in the HPA axis may explain the close relationship between depression and epilepsy. In human and animal models of major depression, abnormal functioning of the HPA axis has long been described[39]. Research has shown that high levels of cortisol in the brain are toxic and lead to degeneration of temporal lobe structures[39]. High levels of cortisol are evident in persons with depression; this may lead to temporal lobe damage, and in turn, epilepsy[39]. A recent study in rats found that increased interictal HPA activity was associated with epilepsy and the severity of depression[39]. At high concentrations, as in situations of chronic stress, glucocorticoids have been associated with damage to the hippocampal formation[39]. In normal circumstances, the hippocampus and amygdala inhibit the HPA axis, however the chronic elevation of glucocorticoids deactivates this inhibition[39]. Suppression of these hormones or the use of anti-depressants has been shown to slow or reverse the degeneration of the hippocampus in persons with depression[46]. A hyperactive HPA axis has also been identified in persons with temporal lobe epilepsy, with glucocorticoid levels as high as those people with only depression[45]. Hippocampal sclerosis is
the most common cause of temporal lobe epilepsy, attributed to neuronal cell loss in the hippocampus, amygdala and other limbic structures; the reduction in size of limbic structures is greater in epilepsy than in persons with major depression[46]. Increased levels of glucocorticoids (caused by a hyperactive HPA axis) may decrease the binding of serotonin and increase levels of glutamate in the synapse—previously described mechanisms that may also relate to the development of depression in epilepsy[40].

1.3.6 Screening for Depression

1.3.6.1 Overview of Depression Screening

Depression is diagnosed by numerous methods in practice, including questionnaires (which are used as surrogate for the diagnosis of major depression or as an indicator for further assessment), structured interviews and clinical judgment based on the DSM[15, 47]. The most commonly used screening questionnaires include the Beck Depression Inventory (BDI I & II)[48, 49], the Center for Epidemiologic Studies Depression Scale (CES-D)[47], the Hospital Anxiety and Depression Scale (HADS)[50], and the Patient Health Questionnaire-9 (PHQ-9)[51]. The Structured Clinical Interview for DSM-IV (SCID) is widely considered the gold standard for depression diagnosis in research [52-54]. DSM diagnostic criteria for major depressive disorder include numerous psychiatric and physical components[15]. Depression screening inventories are based largely on the DSM-IV-TR criteria for depression.

Often, self-report inventories for depression are used in the context of screening. Screening is a method of identifying individuals who have a disorder that is not yet clinically apparent[55, 56]. For screening to be effective, it must meet a certain number of criteria: (a) it should produce a better prognosis than if it were detected and treated later; (b) it should be relatively inexpensive and quick; (c) it should not result in many false positive results, which
could result in inappropriate treatment, increased burden to the health care system and the potential of being stigmatized and labelled; (d) the disease it should be important and prevalent, and cannot be easily detected without screening; and (e) there should be appropriate, available and effective follow-up treatment[55, 56]. If depression is identified and treated sooner in persons with epilepsy, there are less social consequences, the risk of suicide is decreased, and degeneration of limbic structures is slowed.

1.3.6.2 Screening Tools

1.3.6.2.1 HADS

The HADS is a brief, self-report inventory for assessing symptoms of both depression and anxiety[50]. The depressive symptoms of the HADS are different from most scales, as they do not map directly onto the DSM criteria. The questions include “I can laugh and see the funny side of things”, “I feel cheerful”, and “I have lost interest in my appearance”. Each item is scored from 0-3, though the response choices differ for each question. The recommended cutoff for the HADS in persons with epilepsy is 7 or 8 out of 21[57]. One major downside of the HADS is its cost; it is not freely available and a license must be obtained for its use. It still remains one of the few general depression scales that have been validated in persons with epilepsy.

1.3.6.2.2 PHQ-9

The PHQ-9 is a nine-item self-report instrument commonly employed to assess depressive symptoms, and can be used to establish a diagnosis suggestive of major depression, as well as establishing the severity of symptoms[51]. The nine items of the PHQ-9 map directly onto the DSM-5 criteria for major depression[15]. These nine items are: (1) depressed mood, (2) anhedonia, (3) sleeping troubles, (4) appetite changes, (5) feeling guilty or a failure, (6) concentration difficulties, (7) psychomotor agitation or retardation; (8) fatigue; and (9) suicidal
thoughts or acts. All nine items are scored from zero to three: zero indicates the problems did not bother the person at all, one that they were bothered by them several days, two that they were bothered by them more than half of the days, and three that they bothered them nearly every day. The PHQ-9 can be scored in two ways, the cut-point and algorithm methods: in the cut-point method, a total score of 10 or higher (out of 27 total) is indicative of major depression and in the algorithm method at least five symptoms must be endorsed more than half of the days (except suicide, where any score is counted), one of which must be either depressed mood or anhedonia. As a severity measure, scores of 0-4 indicate minimal/no depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 severe depression. The first two items of the PHQ-9 are in themselves considered a tool for assessing depression: the PHQ-2. The PHQ-2 includes only the two cardinal symptoms of depression, anhedonia and depressed mood - the endorsement of one of these symptoms more than half of the days in a two-week period indicate the possibility of major depression.

Critics of the PHQ-9 believe that the somatic symptoms of depression could overlap with common side effects of anti-epileptic medications, invalidating its use in this population[41]. Decreased concentration, fatigue and difficulties sleeping are all anti-epileptic medication side effects that are also questions on the PHQ-9. With this in mind, it is plausible that there could be many false positives on the PHQ-9, as people would endorse somatic symptoms that are a reflection of their medication rather than a mood disturbance. A large number of false positives would lead to decreased specificity and a low positive predictive value; if those conditions existed it would not make an adequate screening tool, though it has yet to be formally validated in this population.
1.3.6.3 Screening for Depression in Epilepsy

In recent years there has been an increase in the number of publications reporting on depression screening in epilepsy, however they lack adequate gold standards or focus on a single depression questionnaire. These studies are summarized below.

Rampling and colleagues evaluated three depression-screening questionnaires in a sample of 266 patients from a specialist clinic in London, England[58]. The HADS, BDI-II and the Neurological Disorders Depression Inventory- Epilepsy (NDDI-E)[59] were compared against a reference standard of another self-report depression questionnaire (the Major Depression Inventory (MDI)). The reported point prevalence of depression based on the MDI was 18.0% (48/266). The lack of a true gold standard (a structured or semi-structured psychiatric interview) limits the applicability of these measures of accuracy and conclusions related to the utility of these scales in screening are not possible.

A 2009 study by Seminario and colleagues employed the PHQ-9 in an effort to screen for depression in a California epilepsy clinic[60]. No attempt to validate the questionnaire was made. In the 263 patients screened, 29.3% reported PHQ-9 scores that indicated a high likelihood of major depression (based on the standard cut-point score of 10/27 total points).

Recently, Gandy and colleagues validated two depression-screening questionnaires (NDDI-E and HADS) in 147 adults at an Australian tertiary care center[61]. Though a semi-structured interview was employed (Mini International Neuropsychiatric Interview (MINI)), only the current major depressive episode and dysthyemic disorder modules were used. It should be noted that the MINI is a brief screening tool for depression, and is not itself a gold standard for diagnosing depression[62]. A study of 174 persons with epilepsy compared MINI diagnoses of depression to those obtained from the SCID interview[62]. The authors found that there was
good concordance (K = 0.86) between the MINI and SCID on the current major depressive episode module, but the concordance was low for other modules. Screening tools for depression may not be sensitive in differentiating depression from bipolar disorder, and some patients may have experienced a past episode of depression or mania, which this version of the MINI would not detect. The authors concluded that due to poor sensitivity (42%), the depression subscale of the HADS could not be used to screen for depression in adults with epilepsy. The sensitivity of the NDDI-E in this population was 84%, and the specificity 78%; a specificity of 78% (ignoring sensitivity) would result in a vast overestimate (due to an increase in false positives) of depression prevalence as compared to the MINI diagnosis. Though, as the authors state, the NDDI-E is superior to the HADS-depression subscale in this population, the tests of diagnostic accuracy do not indicate it would be a useful depression-screening tool in persons with epilepsy.

Data from five tertiary care epilepsy centers across the Unites States are presented in a separate Jones and colleagues’ 2005 paper[63]. One hundred and seventy-four adults with epilepsy were recruited from five universities, using the MINI and SCID mood disorders module as the gold standard, and the BDI-II and CES-D as depression screening tools. It should be noted that the methods of recruitment are not detailed in this manuscript. For example, is difficult to know how recruitment was conducted (e.g. consecutive or not), what the specific inclusion/exclusion criteria were and there is a lack of details related to the depression-assessment procedure (e.g. whether the MINI and SCID were always conducted in the same order). Only the mood disorders module of the SCID was used in this study; it is possible participants could have diagnosable dysthymic or adjustment disorders and screen positive on the depression questionnaires, which would be missed by this version of the SCID. Using the SCID as the gold standard, the sensitivity of the CES-D was 88.5%, specificity 79.1%, negative
predictive value 97.3% and positive predictive value 44.2%. A positive predictive value this low would generally indicate that the CES-D would not perform well as a screening tool for depression in epilepsy. The BDI also demonstrated a low positive predictive value of 55.3% - neither screening tool displays a positive predictive value large enough to indicate its utility as a method for screening for depression in epilepsy.

Through research has been conducted, the ideal tool to screen for depression in persons with epilepsy has not been determined. The questionnaires assessed and validated above have resulted in suboptimal measures of accuracy. Further, adequate validation of multiple depression screening questionnaires has not been conducted using an appropriate gold-standard in a well-described, representative population.

1.3.7 Treating Depression in Epilepsy

1.3.7.1 Psychotropic Effects of Anti-Epileptic Drugs

Many AEDs have known psychotropic effects; carbamazepine, valproic acid, lamotrigine, gabapentin and pregabalin are often associated with positive psychotropic properties while phenobarbital, vigabatrin, topiramate and levetiracetam may be associated with negative psychotropic properties[64, 65]. AEDs should be selected based on their psychotropic effects when considering the treatment of depression in persons with epilepsy[64]. Optimizing AEDs is often the first approach when a patient presents with depression, if, after AEDs are adjusted, the depression persists then pharmacological and non-pharmacological depression treatment options are explored.

1.3.7.2 Pharmacological Management of Depression in Epilepsy

Depression may be under-treated in epilepsy because of fears of lowering the seizure threshold[66] or enhancing AED side-effects, such as weight gain or sexual dysfunction[53]. It is
estimated that no more than 50% of persons with epilepsy with current depression are being
treated, though these studies only explore pharmacological management[43, 62]. Anti-
depressants should be considered as a treatment of choice for depression in epilepsy, taking into
account the current AED regimen[42]. It is recommended to avoid prescribing amoxapine,
clomipramine and bupropion to persons with epilepsy, as they may lower the seizure
threshold[66]. Overall, selective serotonin reuptake inhibitors (SSRIs) and selective
norepinephrine reuptake inhibitors (SNRIs) are associated with low rates of seizures in persons
with epilepsy[66] and in some cases may even increase the seizure threshold[64].

1.3.7.3 Non-Pharmacological Management of Depression in Epilepsy

Non-pharmacological treatments have also been explored for treating depression in
persons with epilepsy. Cognitive behavioral therapy[67] and counseling[68] have been
demonstrated to reduce depressive symptoms in persons with epilepsy in two randomized
controlled trials. Other non-pharmacological treatments for depression in epilepsy include
transcranial magnetic stimulation[69] and vagus nerve stimulation[70]. These stimulation
techniques have been shown to improve depressed mood in persons with epilepsy, though more
studies into their effectiveness are required. Electroconvulsive therapy (ECT) is an effective
method of treating depression alone [81]; interestingly, ECT elicits a seizure, further
complicating the relationship between depression and epilepsy. Non-pharmacologic therapies for
depression in epilepsy show promising results and can be utilized in treating depression in this
population.

1.3.7.4 International Guidelines for Treating Depression in Epilepsy

The Institute of Medicine (IOM) report, Epilepsy Across the Spectrum, published in
2012, recommends interventions aimed at treating depression in epilepsy[71]. Completing these
studies is essential to determine whether these interventions also improve overall health outcomes. The report recommends both pharmacological and non-pharmacological interventions be explored in persons with depression and epilepsy. In addition, they recognize that the majority of research has been conducted in small sample sizes and has largely focused on non-pharmacological management. It is necessary to explore these treatments in large, randomized trials to determine their effectiveness.

An international consensus statement on clinical practice guidelines for the treatment of neuropsychiatric conditions in epilepsy was released in 2011[72]. The working group, established by the ILAE, identified the top 10 clinical areas related to neuropsychiatric conditions in epilepsy; the top area identified was the assessment and management of depressive disorders in epilepsy. The group details 13 practice points to best manage this problem, including: screening for depression using the NDDI-E or PHQ-2 for all new persons with epilepsy or existing patients on an annual basis; the identification and management of mild depressive episodes; employing counselling/psychotherapy combined with antidepressants for treatment; and understanding the psychotropic effects of AEDs and their withdrawal. The authors recommend, among others, that future research focus on improving the detection of neuropsychiatric conditions in epilepsy, developing and validating diagnostic instruments, and effectively translating research findings into clinical practice. These recommendations are consensus-based, rather than fully evidence-based guidelines, developed by experts in the field.

1.4 Knowledge Gaps and Significance

Though much research has been conducted on the topic of depression in persons with epilepsy in recent years, gaps in knowledge still remain. The proportion of persons with depression and epilepsy, and the magnitude of the association between these conditions have
been estimated in the literature, though estimates vary considerably. A pooled estimate of population-based studies on this topic is necessary to quantify the magnitude of effect. An optimal, validated scale for assessing depression in persons with epilepsy has not been definitively established, though recommendations for their use have been put forward. It is necessary to validate screening tools commonly employed in the literature and identify strategies for their appropriate use. There is little literature on the treated prevalence of depression in epilepsy. Estimates from the literature vary, and only focus on pharmacological treatment for depression, excluding non-pharmacological treatment as an option. The studies presented in this dissertation address these knowledge gaps.

1.5 Objectives

1.5.1 Objective 1
To summarize the prevalence of depression in epilepsy as reported in the literature.

1.5.2 Objective 2
To identify, from a set of candidate scales, the diagnostic accuracy of individual depression assessment tools.

1.5.3 Objective 3
To estimate the proportion of those persons with depression in epilepsy who are receiving treatment.

The above thesis objectives were accomplished by conducting three studies. For objective 1, a systematic review and meta-analysis of population-based studies of depression in epilepsy was conducted and this study is reported in Chapter 2. Chapter 3 describes the results of a study addressing objective 2, validating depression screening tools for use in persons with epilepsy and
identifying their diagnostic accuracy in this population. Finally, Chapter 4 presents the findings of objective 3—estimating how many currently depressed persons with epilepsy are receiving treatment for depression.

1.6 Thesis Outline

This thesis examines the relationship between depression and epilepsy, using multiple methodologies and data sources. First, a systematic review and meta-analysis of population-based studies on depression and epilepsy was conducted to quantify the prevalence and magnitude of association. Data from a large, consecutive sample of persons with epilepsy were used for the next analyses, which focus on validating screening tools for depression and estimating the treated prevalence of depression in this population.

This chapter has provided background information on the topic of depression and epilepsy, with an introduction to the tools used to measure depression and the different methods of treatment. It briefly discusses current gaps in knowledge and provides a justification for the research conducted in the three chapters. The following three chapters represent: (1) a unique publication, (2) a manuscript currently submitted for publication, and (3) a manuscript formatted and ready to be submitted for publication. Each chapter is linked by the theme of further elucidating the relationship between depression and epilepsy. Paper 1 will frame the remaining objectives by providing an estimate of the burden of disease in the general population. Papers 2 and 3 will provide information necessary to plan new approaches to the problem of depression in persons with epilepsy (through earlier or more effective detection, prevention through risk factor modification, improved access or enhanced therapeutic strategies). Finally, there will be a general discussion of the findings of the three manuscripts, followed by considerations of the
challenges in conducting this research, clinical and public health implications and directions for future research.
CHAPTER 2: DEPRESSION IN EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS
2.1 ABSTRACT

Objective: To estimate the prevalence of depression in persons with epilepsy (PWE) and the strength of association between these two conditions.

Methods: The MEDLINE (1948-2012), EMBASE (1980-2012) & PsycINFO (1806-2012) databases, reference lists of retrieved articles and conference abstracts were searched. Content experts were also consulted. Two independent reviewers screened abstracts and extracted data. For inclusion, studies were population-based, original research, and reported on epilepsy and depression. Estimates of depression prevalence among PWE and of the association between epilepsy and depression [estimated with reported odds ratios (OR)] are provided.

Results: Of 7,106 abstracts screened, 23 articles reported on 14 unique data sources. Nine studies reported on 29,891 PWE who had an overall prevalence of active depression of 23.1% (95% confidence interval [CI]: 20.6%-28.31%). Five of the 14 studies reported on 1,217,024 participants with an overall OR of active (current or past-year) depression of 2.77 (95% CI: 2.09-3.67) in PWE. For lifetime depression, four studies reported on 5,454 PWE, with an overall prevalence of 13.0% (95% CI: 5.1-33.1) and three studies reported on 4,195 participants with an overall OR of 2.20 (95% CI: 1.07-4.51) for PWE.

Conclusions: Epilepsy was significantly associated with depression and depression was observed to be highly prevalent in PWE. These findings highlight the importance of proper identification and management of depression in PWE.
2.2 Introduction

Epilepsy has an estimated prevalence of approximately 5.0 per 1000 persons in North America\textsuperscript{1-3}, and is associated with an increased risk of numerous psychiatric symptoms and comorbidities, such as suicidality, anxiety and depression.\textsuperscript{4,5} Recent research has focused on the association between epilepsy and depression, the latter being the leading cause of years lived with disability and the fourth leading cause of disability-adjusted life years worldwide.\textsuperscript{6}

Depression is often under-recognized and improperly managed in persons with epilepsy (PWE), and can interfere with treatment outcomes and quality of life.\textsuperscript{7} Under-managed depression in epilepsy may also lead to missed work, increased health-care system utilization, and direct medical costs.\textsuperscript{8} The reported prevalence of depression in PWE varies between 12 and 37\% in community settings.\textsuperscript{9,10} This wide range may be attributed to study design, population demographics, or the method of diagnosing depression and/or epilepsy.

A systematic review and meta-analysis could help explain the variability in the existing literature and through pooling, produce more precise estimates. The purpose of this systematic review was to estimate the prevalence of depression in PWE and to determine the strength of the association between epilepsy and depression. The final objective was to assess the nature and importance of heterogeneity between estimates.

2.3 Methods

2.3.1 Search Strategy

The systematic review and meta-analysis was conducted according to a pre-determined protocol and established guidelines (MOOSE).\textsuperscript{11} The search strategy (Appendix 1) was based on input from the co-authors, key articles, and consultation with a medical librarian with systematic review expertise. No restrictions were placed on time of publication or language. The search was
executed on January 16, 2012 in the electronic databases Medline, EMBASE, and PsycINFO and references were exported and managed using EndNote X5. Bibliographies of included articles and proceedings from the past three years of relevant conferences (American Psychiatric Association, American Academy of Neurology and American Epilepsy Society) were manually searched for additional articles. Experts in psychiatry (SP) and epileptology (NJ & SW) were asked to identify any missing key publications and provide information on unpublished or ongoing studies.

2.3.2 Study Selection

Two reviewers (JD & KF) independently screened titles and abstracts to identify those reporting on original research that involved people with epilepsy and depression or psychiatric comorbidities. Abstracts that were clearly not population-based (eg. case series and clinic-based) were excluded at this stage. The initial screen was intentionally broad to capture all relevant literature.

Two reviewers (JD & KF) independently screened the full-length articles of abstracts identified in the first screen. Articles were included if they met the following criteria: i) original research, ii) cohort or cross-sectional design, iii) population-based (probability sampling, survey of entire population, or included all healthcare providers of a specific population of known size [eg. all general practitioners in Cardiff]), iv) reported an odds ratio (or sufficient information to calculate an odds ratio) of depression in PWE relative to those without epilepsy, and v) reported a prevalence of depression in PWE or sufficient information to calculate an estimate. Articles solely using drug prescriptions to ascertain depression or epilepsy were excluded as antiepileptic and antidepressant drugs are both used in the treatment of unrelated conditions and would not provide a reliable estimate. All non-English articles were screened in the same fashion using
Google Translate and colleagues fluent in the respective language were involved as necessary. Abstracts and unpublished studies were also considered. Disagreements of eligibility were resolved through discussion and involvement of a third party (SP, NJ, & SW) as necessary.

2.3.3 Data Extraction and Study Quality

Two reviewers (JD & KF) extracted and reached agreement on data from included articles using a standard electronic data form. Information from multiple articles reporting on the same data source was combined. For example, numerous studies reported on the Canadian Community Health Survey (CCHS); study characteristics and estimates were abstracted from all articles reporting on the CCHS to ensure the most comprehensive assessment. Studies reporting the most detailed description of methodology and results were extracted; other studies reporting on the same data source were used to ensure consistency and accuracy. The following data were extracted: study information (author, year), population demographics (age, location, time of data collection), condition information (data sources, condition definition, total number of participants), population size, and reported estimates (prevalence, odds ratio) or the information needed to calculate an estimate. Indicators of study quality, which informed the assessment of condition heterogeneity, were extracted relating to sample representativeness, condition assessment, and statistical methods.

2.3.4 Data Synthesis and Analysis

To assess for significant between-study heterogeneity, the Cochrane Q statistic was calculated and $I^2$ was used to quantify the magnitude of between-study heterogeneity. When statistically significant heterogeneity ($Q$ statistic $p$-value of < .05) was absent the pooled estimate and 95% confidence intervals were calculated using a fixed-effects model. When significant heterogeneity was present a random-effects model was used. Publication bias was investigated visually using
funnels plots and statistically using Begg’s, Egger’s, and the trim and fill tests.\textsuperscript{16-19} The trim and fill method identifies funnel plot asymmetry by imputing the effect estimates of potentially missing studies and assessing the influence of these studies on the pooled estimate.\textsuperscript{17, 18}

Current depression and depression in the past 12 months were combined representing a measure of active depression. Lifetime depression was considered separately. Due to the limited number of studies on lifetime depression, only studies reporting active depression were investigated for potential sources of heterogeneity by stratifying on the method for ascertaining depression and how epilepsy was diagnosed. When studies provided estimates that were both not adjusted and adjusted for confounders, the unadjusted estimate was used due to the variability in confounders. For all tests, \( p<0.05 \) was deemed to be significant. Combined OR, prevalence and 95\% CIs were calculated separately for lifetime and active depression. All statistical analyses were carried out in R version 2.14.\textsuperscript{20} The meta package was used to produce the pooled estimates, forest plots, and publication bias assessment.\textsuperscript{21} The metafor package was used to conduct the meta-regression using restricted maximum likelihood estimation.\textsuperscript{22}

2.4 Results

2.4.1 Identification & Description of Studies

The results of the search strategy yielded a total of 9,048 citations: 3,533 from Medline, 4,438 from EMBASE and 1,077 from PsycINFO (a total of 7,106 after duplicates removed) (Figure 2.1). After the initial screen, 166 articles met the criteria for full-text review, of which 143 were excluded (39 abstract only, 7 duplicate studies, 16 not original research, 40 not population-based, 2 no depression definition & 39 no depression estimate). From the 23 eligible articles, 14 unique data sources were included in the meta-analysis. For active depression, five studies reported an
OR and nine reported prevalence. For lifetime depression, three studies reported an OR and four reported prevalence.

Characteristics of the 14 included studies are shown in Table 2.1. Four studies reported lifetime depression, six reported depression in the past 12 months, and four reported on current (past 30 days) depression. Dates of publication ranged from 1996-2011. Seven of 14 studies reported summary data on age, with the mean age of participants ranging from 37.2-52.4 years. Eight studies were based in North America, four in Europe, and one each in Asia and South America.

Diagnosis of epilepsy varied with studies using self-report (whether diagnosed by health professional or not), chart review or administrative data codes. Depression was diagnosed by one of three different scales, self-report, administrative data codes or clinical assessment. Three data sources employed the Hospital Anxiety and Depression Scale (HADS)\textsuperscript{23-29}, one used the Center for Epidemiologic Studies-Depression Scale (CES-D)\textsuperscript{8, 9, 30, 31}, and a final study used the Kessler-6 (K-6).\textsuperscript{32} The K-6 was included with the remaining data sources, as it has a question specific to feeling depressed in the past 30 days.\textsuperscript{33} Two studies using self-report of depression included one with\textsuperscript{34} and one without\textsuperscript{7} a clarifier of health professional diagnosis.

The administrative data codes used to determine depression diagnosis varied widely (Appendix 2); with four studies using International Classification of Diseases codes (ICD-9 or ICD-10), International Classification of Primary Care (ICPC) codes or read codes.\textsuperscript{35-38} Three studies used a clinical assessment to ascertain depression status: the Canadian Community Health Survey (CCHS) 1.1\textsuperscript{39} used the World Mental Health-Composite Diagnostic Interview (WMH-CIDI) Short Form, the CCHS 1.2\textsuperscript{5, 40} employed a Canadian adaptation of the WMH-CIDI, and the study of the Iranian population\textsuperscript{10} used the Structured Clinical Interview for DSM-IV.
2.4.2 Study Quality Assessment

The quality of the included studies varied (Table 2.2). Seven of 10 eligible studies reported a response rate ≥70% and only 2 studies clearly described non-responders. All studies used standardized methods to collect data on depression, with 10 using validated criteria to assess the presence of depressive symptoms. Thirteen studies (1 was unclear) used standardized methods for data collection and 9 used a standard accepted classification of epilepsy. Only five studies adjusted for potential confounders and the number of confounders varied (Table 2.1).

2.4.3 Active Depression in Persons with Epilepsy

The prevalence of active depression in PWE across the 9 studies reporting on 29,891 persons ranged from 13.2%-36.5% (Figure 2.2). The overall pooled prevalence of active depression was 23.1% (95% CI: 19.8%-27.0%) (Figure 2.2). In the five studies that reported on the OR of active depression (odds of active depression in PWE relative to the odds of active depression in persons without epilepsy), the number of participants was 1,217,024 with an estimated pooled OR of 2.77 (95% CI: 2.09-3.67) using a random-effects model (Figure 2.3). Four studies reported an adjusted OR of active depression varying in magnitude and in adjustment for various confounders. Adjusting for age and sex, the CCHS 1.2 reported an OR of 2.3 (95% CI: 0.99-5.23)\(^5\), the CCHS 1.1\(^39\) adjusted for gender, education level, marital status, race, immigration status and food security and reported an adjusted OR of 1.43 (95% CI: 1.13-1.82); the California Health Interview Survey\(^32\) reported 2 adjusted models, Model 1 reported an OR of 3.49 (95% CI:2.96-4.12), after adjusting for gender, age, race/ethnicity, annual household income, education attainment and urban/rural living status. Model 2 adjusted for all Model 1 factors, as well as numerous comorbid health conditions, with an OR of 3.14 (95% CI: 2.42-4.07); the
HealthStyles Survey adjusted for income and race/ethnicity, with a reported OR of 2.40 (95% CI: 1.40-4.30).

2.4.4 Lifetime Depression in Persons with Epilepsy

Four studies reported prevalence of lifetime depression in PWE ranging from 4.1%-32.5%. Overall there were 5,454 PWE with an overall prevalence of 13.0% (95% CI: 5.1%-33.1%) (Figure 2.6). The OR of lifetime depression in PWE was reported by three studies at 1.48 (95% CI: 1.37-1.59), 1.80 (95% CI: 1.01-3.20) and 3.96 (95% CI: 2.96-5.29) (Figure 2.7). Overall, these studies reported on 4,195 persons with an OR of lifetime depression of 2.20 (95% CI: 1.07-4.51). Significant heterogeneity was found in the meta-analyses of lifetime depression for both OR and prevalence estimates. Only one study reported an OR of 1.80 (95% CI: 1.1-3.2), adjusting for age and sex, and was not included in the meta-analysis.

2.4.5 Sources of Heterogeneity

Prevalence estimates, when stratified by method of depression diagnosis, were slightly greater when based on self-report and K-6 measures than in studies using validated depression scales or administrative data codes (Figure 2.4). When stratified by depression diagnostic method, ORs estimates varied between methods (Figure 2.5). The estimates for the CES-D and K-6 scales (which measure distress more broadly, with sub-elements related to depression) were slightly higher than those using validated depression-only scales. The estimates of active prevalence of depression did not differ when stratified by method of epilepsy diagnosis, (Figure 2.8). When stratified by the method of epilepsy diagnosis, the individual study estimates of the OR for active depression using administrative data codes of epilepsy diagnosis were slightly lower than those using self-report for epilepsy diagnosis (Figure 2.9).
2.4.6 Publication Bias

Neither the overall OR nor prevalence estimates had significant publication bias detected by either Begg’s or Egger’s tests. However, on visual inspection the funnel plot for the estimated OR appeared asymmetrical. This was supported by the trim and fill method identifying two small missing studies with imputed ORs of 1.17 (95% CI: 0.78-1.76) and 1.09 (95% CI: 0.77-1.55). The pooled OR after the imputation using a random-effects model was 2.20 (1.48-3.27). On visual inspection the prevalence funnel plot appeared symmetrical and no missing studies were found using the trim and fill method.

2.5 Conclusion

This is, to our knowledge, the first systematic review and meta-analysis of the association between depression and epilepsy in population-based studies. Based on the combination of more than one million participants we found an almost three-fold increase in the odds of active depression in PWE compared to those without epilepsy. Even with a conservative interpretation, PWE have two-fold increased odds of active depression. Additionally, approximately one in four people with epilepsy were found to have active depression. The odds of lifetime depression in PWE was increased two-fold as compared to those without epilepsy. The prevalence was high, approaching thirteen percent. It should be noted that the ICPC codes used in the Nuyen study have not been validated in depression or epilepsy. When this study was excluded, the prevalence of lifetime depression in epilepsy was almost twenty percent. The lifetime prevalence studies reported greater variation in estimates of depression in PWE. In addition, none of the reported ORs crossed the null value and thus, demonstrate a consistent and significant association of epilepsy with depression. These population-based studies represent the burden of depression in all patients with epilepsy rather than in any one selected clinical population.
Three studies used a clinical assessment for the diagnosis of depression and there were six different methods of depression diagnosis across the nine studies reporting a prevalence of active depression. The K-6\textsuperscript{33} and CES-D\textsuperscript{43} include measures of depressive symptoms, but are also considered to be broad measures of psychological distress, perhaps accounting for their relatively greater ORs and prevalence estimates. Differences in the method of depression diagnosis also makes it difficult to generalize findings across OR and prevalence estimates, as similarities between studies are lacking.

When comparing unadjusted vs. adjusted OR estimates, the unadjusted estimates tended to be higher. It is possible that the studies that adjusted for over four confounding variables were actually removing the effect of some of the factors that would mediate the relationship between epilepsy and depression. That is, by adjusting for factors that may be more common in persons with epilepsy, or consequences of having epilepsy, the effect of epilepsy on depression may be masked. Some of the factors controlled for as confounders may in fact be on the causal pathway between epilepsy and depression, and as such not true confounders. People with epilepsy may experience more of these factors (single marital status, lower education, less food security), and as such the relationship between epilepsy and depression is partially removed. Adjusted OR estimates may not represent the true population value, and should be interpreted separately.

It has been hypothesized that the relationship between epilepsy and depression is bidirectional.\textsuperscript{44} Epilepsy may affect the development of depression through chronic stress exposure, in which stressful life events and inherent vulnerability affect the likelihood of developing depression.\textsuperscript{45} The uncertainty and unpredictability of seizures may induce learned helplessness\textsuperscript{46}, where persons with epilepsy report less personal control over their health than their peers.\textsuperscript{47, 48} Conversely, depression may facilitate the development of epileptic activity; proposed
mechanisms of action for this association include hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and disturbances of glutamate and GABA neurotransmitters. A hyperactive HPA axis has been found in both epilepsy and depression and may lead to substantive cortical changes, particularly in the volume of the hippocampus and frontal lobes. Social factors, such as a lack of occupational attainment, social engagement, or social support, may also influence the relationship between epilepsy and depression.

Our study searched three large online databases, with no restrictions placed on language or date of publication. The meta-analysis included data from over one million participants and over 30,000 persons with epilepsy. However, the strength of the inference afforded by our analysis may be limited by the following factors: First, the quality of the included studies was not always optimal, demonstrated by the lack of reporting of non-responders and the lack of use of validated depression diagnostic criteria in some studies, though the magnitude of this problem may be small, and is unlikely to substantially alter our conclusion. Second, there was heterogeneity of OR and prevalence estimates across studies, this could be in part due to heterogeneity in the method of diagnosis of both depression and epilepsy. Nevertheless the final stratified analysis showed pooled ORs consistently greater than one over numerous clinical factors. Third, there was a lack of consistency in terms of how depression and epilepsy were diagnosed. Finally, the funnel plots showed some asymmetry, indicating the possibility of publication bias. When the trim and fill analysis was conducted, the overall imputation did not change the general result (though the strength of the OR was attenuated), suggesting the results are robust to the possibility of unpublished negative studies. Though limitations are present we do not believe they hinder the conclusion that epilepsy is associated with significantly increased odds of depression.
This systematic review and meta-analysis found significantly increased odds of active and lifetime depression in persons with epilepsy relative to those without epilepsy. These findings were consistent, regardless of the method of depression and epilepsy diagnosis. The focus on population-based studies allows for the results to be more applicable to primary care. Physicians responsible for the care of persons with epilepsy should be aware of the increased odds of depression and screen patients appropriately. Future research should focus on identifying the mechanisms of increased depression among persons with epilepsy and appropriate targeted interventions.

2.6 References


<table>
<thead>
<tr>
<th>Study</th>
<th>Country, Continent</th>
<th>Data Source</th>
<th>Depression Diagnosis</th>
<th>Depression Time Period</th>
<th>Epilepsy Diagnosis</th>
<th>Reports Odds Ratio</th>
<th>Reports Prevalence</th>
<th>Reports Adjusted Odds Ratio</th>
<th>Adjusted For</th>
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<td>CCHS 1.2&lt;sup&gt;5,40&lt;/sup&gt;</td>
<td>Canada, NA</td>
<td>Two stage stratified random sampling of Canadian population</td>
<td>WMH-CIDI</td>
<td>Lifetime</td>
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<td>USA, NA</td>
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<td>At least two outpatient or one inpatient visit(s) coded with ICD-9 296.2 or 296.3</td>
<td>12-Month (fiscal year of 1999)</td>
<td>At least one inpatient or outpatient visit coded with ICD-9 345.xx or 780.3 and AED at least once during the year</td>
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<td>Dutch National Survey of General Practices&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Netherlands, Europe</td>
<td>134 GPs working in 75 General Practices</td>
<td>ICPC Code P76</td>
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<td>Iranian Nationwide Study&lt;sup&gt;10, 42&lt;/sup&gt;</td>
<td>Iran, Asia</td>
<td>Randomized cluster sampling of Iranian population</td>
<td>Schedule for Affective Disorders and Schizophrenia (SADS) and DSM-IV criteria applied by clinical psychologist</td>
<td>Lifetime</td>
<td>Epilepsy Questionnaire – two or more unprovoked nonfebrile seizures</td>
<td>Epilepsy: 454</td>
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<td>Study</td>
<td>Country/Country Region</td>
<td>Study Design</td>
<td>Data Collection Method</td>
<td>Data Source</td>
<td>Diagnosis Validation</td>
<td>Data Collection Period</td>
<td>Definition of Epilepsy</td>
<td>Definition of No Epilepsy</td>
<td>Gender, Education Level, Marital Status, Race/Ethnicity, Annual Household Income, Education Attainment, Urban/Rural</td>
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<td>211 General Practices</td>
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<td>Read code equivalent of ICD-9 311 12-month (previous 6 months)</td>
<td>Read code equivalent of ICD-9 345</td>
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<td>USA, NA</td>
<td>Mailed questionnaire to households randomly sampled from maintained survey panels</td>
<td>Self-Report of diagnosis by a Health Professional</td>
<td>Lifetime</td>
<td>Self-Report of diagnosis by a Health Professional</td>
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<td>California, USA, NA</td>
<td>Geographically stratified, random-digit dialed, multistage telephone survey</td>
<td>Current (past 30 days)</td>
<td>Self-Report of diagnosis by a Health Professional</td>
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<td>Method</td>
<td>Data Collection</td>
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<td>Health Professional Diagnosis</td>
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<td>Race/Ethnicity</td>
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<td>Mailed survey using stratified random sampling from maintained survey panels</td>
<td>Self-Report</td>
<td>12-month</td>
<td>Self-Report of diagnosis by a Health Professional</td>
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<td>NFO Survey</td>
<td>USA, NA</td>
<td>Mailed survey to representative sample of panel held by NFO</td>
<td>Center for Epidemiology Studies-Depression Scale (CES-D) score of 15 or above</td>
<td>12-month</td>
<td>Self-Report of diagnosis by a Health Professional</td>
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<td>No Epilepsy: 362</td>
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<td>Brazilian Community Survey</td>
<td>Brazil, SA</td>
<td>Target population door-to-door survey screening with confirmation of cases by neurologist</td>
<td>HADS with 7 positive items</td>
<td>Current</td>
<td>Diagnosis by Neurologist</td>
<td>Epilepsy: 153</td>
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<tr>
<td>Mersey General Practices</td>
<td>England, Europe</td>
<td>31 general practices randomly selected to be representative of the Mersey region</td>
<td>HADs score of 8 or above</td>
<td>Current</td>
<td>Seizure in the past 2 years or seizure-free and on AEDs</td>
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<td>Epilepsy: 7253</td>
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<tr>
<td>Calgary Administrative Databases</td>
<td>Alberta, Canada, NA</td>
<td>5 Linked Databases (Discharge Abstract Database, Ambulatory Care Classification System, Alberta)</td>
<td>ICD-9 Codes 296.2, 296.3, 296.5, 300.4, 309.x, 311.x or ICD-10 Codes F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2,</td>
<td>12-Months</td>
<td>ICD-9 Code 345 or ICD-10 Codes G40-G41</td>
<td>Epilepsy: 7253</td>
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<td></td>
</tr>
</tbody>
</table>

Income, race/ethnicity
| Cardiff General Practices<sup>26, 27, 29</sup> | Wales, Europe | 40 general practices from Cardiff region used to identify patients who then completed mailed surveys | HADS score of 8 or higher | Current | Read codes identifying recurrent seizures and AED prescription in the past 6 months | Epilepsy: 515 | N | Y | N |

CCHS = Canadian Community Health Survey; LHS = Large Health Survey of VA Enrollees; GPRD = General Practice Research Database; EPIC = Epilepsy Comorbidities and Health; CHIS = California Health Interview Survey; NFO = National Family Opinion; NA= North America; Y=Yes; N=No; HADS= Hospital Anxiety and Depression Scale; AED= Anti-epileptic Drug; ICD= International Classification of Disease; WMH-CIDI= World Mental Health-Composite Diagnostic Interview; ICPC= International Classification of Primary Care; DSM= Diagnostic and Statistical Manual of Mental Disorders
Figure 2.1 Flowchart of Studies from the Systematic Review

Number Identified through Medline (n=3533) → Number Identified through EMBASE (n=4438) → Number Identified through PsycINFO (n=1077) → Records after Duplicates Removed (n=7106)

Records screened (n=7106) → Records excluded (n=6946)

Full text articles identified by hand searching or expert consultation (n=0)

Records excluded:
- Abstract Only (n=39)
- Duplicates (n=7)
- Not original research (n=16)
- Not population-based (n=40)
- No depression definition (n=2)
- No depression estimate (n=39)

Full-text articles assessed for eligibility (n=166)

Eligible studies meeting inclusion criteria (n=23)

Number of unique data sources (n=14)

Active Depression Prev (n=9) → Active Depression OR (n=5) → Number of unique data sources (n=14) → Lifetime Depression OR (n=3) → Lifetime Depression Prev (n=4)
Figure 2.2 Overall Prevalence (%) of Active Depression among Persons with Epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Health Survey (LHS)</td>
<td>21.61</td>
<td>[20.94; 22.31]</td>
</tr>
<tr>
<td>Calgary Admin Data</td>
<td>28.18</td>
<td>[27.16; 29.24]</td>
</tr>
<tr>
<td>NFO Survey</td>
<td>36.50</td>
<td>[33.26; 40.05]</td>
</tr>
<tr>
<td>CCHS 1.1</td>
<td>13.17</td>
<td>[11.07; 15.68]</td>
</tr>
<tr>
<td>Mersey</td>
<td>25.00</td>
<td>[21.98; 28.43]</td>
</tr>
<tr>
<td>Cardiff GPs</td>
<td>27.80</td>
<td>[24.19; 31.95]</td>
</tr>
<tr>
<td>Brazilian Community Survey</td>
<td>20.92</td>
<td>[15.37; 28.46]</td>
</tr>
<tr>
<td>GPRD</td>
<td>18.22</td>
<td>[17.26; 19.24]</td>
</tr>
<tr>
<td>HealthStyles</td>
<td>35.11</td>
<td>[27.82; 44.32]</td>
</tr>
<tr>
<td><strong>Pooled Totals</strong></td>
<td><strong>24.13</strong></td>
<td><strong>[20.56; 28.31]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2$=97.7%, $Q$=351.3, df=8, $p<0.0001$
Figure 2.3 Overall Odds Ratio of Active Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFO Survey</td>
<td>4.30</td>
<td>[3.02; 6.10]</td>
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<tr>
<td>CCHS 1.1</td>
<td>1.84</td>
<td>[1.47; 2.31]</td>
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<tr>
<td>CHIS</td>
<td>4.01</td>
<td>[2.66; 6.04]</td>
</tr>
<tr>
<td>GPRD</td>
<td>2.16</td>
<td>[2.02; 2.31]</td>
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<tr>
<td>HealthStyles</td>
<td>2.92</td>
<td>[2.02; 4.22]</td>
</tr>
<tr>
<td><strong>Pooled Totals</strong></td>
<td><strong>2.77</strong></td>
<td><strong>[2.09; 3.67]</strong></td>
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</table>

Heterogeneity: I-squared=85.1%, Q=26.9, df=4, p<0.0001
Figure 2.4 Overall Prevalence (%) of Active Depression among Persons with Epilepsy by Depression Diagnostic Tool

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Admin Codes</td>
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</tr>
<tr>
<td>Large Health Survey (LHS)</td>
<td>21.61</td>
<td>[20.94; 22.31]</td>
</tr>
<tr>
<td>Calgary Admin Data</td>
<td>28.18</td>
<td>[27.16; 29.24]</td>
</tr>
<tr>
<td>Pooled Totals</td>
<td>24.68</td>
<td>[19.03; 32.00]</td>
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<tr>
<td>Heterogeneity: $i^2=99.1%$, $Q=114.2$, df=1, $p=0.0001$</td>
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<td>NFO Survey</td>
<td>36.50</td>
<td>[33.26; 40.05]</td>
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<tr>
<td>Pooled Totals</td>
<td>36.50</td>
<td>[33.26; 40.05]</td>
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<td>CIDI–SFMD</td>
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<td>[11.07; 15.68]</td>
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<tr>
<td>Pooled Totals</td>
<td>13.17</td>
<td>[11.07; 15.68]</td>
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<td>Heterogeneity: $i^2=NaN%$, $Q=0$, df=0, $p=1$</td>
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<td>HADs</td>
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<td>Mersey</td>
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<td>[21.98; 28.43]</td>
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<tr>
<td>Cardiff GPs</td>
<td>27.80</td>
<td>[24.19; 31.95]</td>
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<td>Brazilian Community Survey</td>
<td>20.92</td>
<td>[15.37; 28.46]</td>
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<tr>
<td>Pooled Totals</td>
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<td>[22.61; 28.80]</td>
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<td>[17.26; 19.24]</td>
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<td>[27.82; 44.32]</td>
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<td>35.11</td>
<td>[27.82; 44.32]</td>
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<td>[20.56; 28.31]</td>
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<td>Heterogeneity: $i^2=37.7%$, $Q=351.3$, df=8, $p=0.0001$</td>
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Figure 2.5 Overall Odds Ratio of Active Depression by Depression Diagnostic Tool
<table>
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<th>Source</th>
<th>Target Population Clearly Defined?</th>
<th>Probability or Entire Population Sampled?</th>
<th>Response Rate &gt; or = 70% (if applicable)?</th>
<th>Non-Responders Clearly described?</th>
<th>Sample Representative of target population?</th>
<th>Data Collection Methods Standardized for Depression?</th>
<th>Validated criteria to assess presence/absence of Depression?</th>
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<td>Year</td>
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</table>

*NR= Not Reported; U= Unclear; NA= Not Applicable
Appendix 1. Search Strategy

MEDLINE:

1. mental disorders/
2. exp mood disorders/
3. mental health/
4. mental health services/
5. exp depression/
6. (depression or depressive or depressed or psychiatric or mental health).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Epilepsy
9. (seizure* or epilepsy or convuls* or epileptic*).tw.
10. 8 or 9
11. exp Epidemiologic Methods/
12. exp Epidemiology/
13. exp Population
14. (prevalence or incidence or epidemiolog* or population or community).tw.
15. 11 or 12 or 13 or 14
16. 7 and 10 and 15
17. Remove Animal Only Studies

PsycINFO:

1. mental disorders/
2. exp affective disorders/
3. exp “depression (emotion)”/
4. exp mental health/
5. (depression or depressive or depressed or psychiatric or mental health).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Epilepsy/
8. (seizure* or epilepsy or convuls* or epileptic*).tw.
9. 7 or 8
10. exp epidemiology/
11. exp population/
12. (prevalence or incidence or epidemiolog* or population or community).tw.
13. 10 or 11 or 12
14. 6 and 9 and 13
15. Remove Animal Only Studies
EMBASE:

1. mental disease/
2. exp emotional disorder/
3. mood disorder/
4. mental health/
5. mental health care/
6. exp depression/
7. exp major affective disorder/
8. exp minor affective disorder/
9. (depression or depressive or depressed or psychiatric or mental health).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Epilepsy/
12. (seizure* or epilepsy or convuls* or epileptic*).tw.
13. 11 or 12
14. exp epidemiological data/
15. exp epidemiology/
16. exp "population and population related phenomena"/
17. (prevalence or incidence or epidemiolog* or population or community).tw.
18. 14 or 15 or 16 or 17
19. 10 and 13 and 18
20. Remove Animal Only Studies
Appendix 2. Administrative Data Codes for Depression Diagnosis

ICD-9

- 296.2: Major Depressive Disorder, Single Episode
- 296.3: Major Depressive Disorder, Recurrent Episode
- 296.5: Bipolar I Disorder, Most Recent Episode Depressed
- 300.4: Dysthymic Disorder
- 309.x: Adjustment Reaction
- 311.x: Depressive Disorder, Not Elsewhere Classified

ICD-10

- F20.4: Post-Schizophrenic Depression
- F31.3-F31.5: Bipolar Disorder, Most Recent Episode Depressed
- F32.x: Mild Depressive Episode
- F33.x: Recurrent Depressive Disorder
- F34.1: Dysthymia
- F41.2: Mixed Anxiety and Depressive Disorder
- F43.2: Adjustment Disorder

ICPC

- P76: Depressive Disorder
Figure 2.6. Prevalence (%) of Lifetime Depression in Persons with Epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Prop (in %)</th>
<th>95%-CI</th>
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<tbody>
<tr>
<td>CCHS 1.2</td>
<td>17.40</td>
<td>[13.30; 22.76]</td>
</tr>
<tr>
<td>Iranian Nationwide Study</td>
<td>12.11</td>
<td>[9.46; 15.52]</td>
</tr>
<tr>
<td>Dutch National GP Survey</td>
<td>4.05</td>
<td>[3.10; 5.30]</td>
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<tr>
<td>EPIC</td>
<td>32.50</td>
<td>[30.98; 34.09]</td>
</tr>
<tr>
<td><strong>Pooled Totals</strong></td>
<td><strong>12.97</strong></td>
<td><strong>[5.08; 33.12]</strong></td>
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</tbody>
</table>

*Heterogeneity: I-squared=95%, Q=289.3, df=3, p<0.0001*
Figure 2.7. Odds Ratio of Lifetime Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
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<tr>
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<td>[1.01; 3.20]</td>
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<td>[2.96; 5.29]</td>
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<td>[1.37; 1.59]</td>
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<tr>
<td><strong>Pooled Totals</strong></td>
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<td>[1.07; 4.51]</td>
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</table>

Heterogeneity: I²=squared=95.2%, Q=42.1, df=2, p=0.0001

OR of Depression Among Persons with Epilepsy
Figure 2.8. Prevalence (%) of Active Depression in Persons with Epilepsy, Stratified by Method of Epilepsy Diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Large Health Survey (LHS)</td>
<td>21.61</td>
<td>[20.94; 22.31]</td>
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<td>Calgary Admin Data</td>
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<td>[27.16; 29.24]</td>
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<tr>
<td>Pooled Totals</td>
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<td>[19.03; 32.00]</td>
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<tr>
<td><strong>Neurologist Diagnosis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Brazilian Community Survey</td>
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<td>[15.37; 28.46]</td>
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<td>Pooled Totals</td>
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<td><strong>Read Codes</strong></td>
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<tr>
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<td>[21.98; 28.43]</td>
</tr>
<tr>
<td>Cardiff GPs</td>
<td>27.50</td>
<td>[24.19; 31.95]</td>
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<tr>
<td>GPRD</td>
<td>18.22</td>
<td>[17.26; 19.24]</td>
</tr>
<tr>
<td>Pooled Totals</td>
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<td>[17.42; 30.66]</td>
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<td><strong>Self-Report</strong></td>
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<tr>
<td>CCHS 1.1</td>
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<td>[11.07; 15.68]</td>
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<tr>
<td>HealthStyles</td>
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<td>[27.82; 44.32]</td>
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<td>NFO Survey</td>
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<td>[33.26; 40.05]</td>
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<td>[13.16; 50.03]</td>
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<td><strong>Pooled Totals</strong></td>
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<td>[20.56; 28.31]</td>
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Heterogeneity: $I^2$ varies, all $Q > 0$, $df > 0$, $p < 0.0001$
Figure 2.9. Odds Ratio of Active Depression, Stratified by Method of Epilepsy Diagnosis

<table>
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<tr>
<th>Study</th>
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<td><strong>Self–Report</strong></td>
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<td>[1.47; 2.31]</td>
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<tr>
<td>Pooled Totals</td>
<td>3.05</td>
<td>[1.96; 4.75]</td>
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*Heterogeneity: I-squared=86%, Q=21.5, df=3, p<0.0001*

**Pooled Totals** 2.77 [2.09; 3.67]

*Heterogeneity: I-squared=65.1%, Q=26.9, df=4, p<0.0001*

OR of Active Depression Among Persons with Epilepsy
CHAPTER 3: SCREENING TOOLS FOR DEPRESSION IN EPILEPSY
3.1 Abstract

Objective: Depression is a common comorbidity of epilepsy and its timely identification in persons with epilepsy is essential. The use of screening tools to detect depression is common in epilepsy, but scales in current use have not been validated using a gold standard in this population. The present study aims to validate three commonly used depression screening scales and assess new cut-points for scoring for those with epilepsy.

Methods: Persons with epilepsy (n=185) from the only epilepsy clinic in a large urban health region completed questionnaires (e.g. socio-demographics, adverse event profile) and three depression screening tools (Hospital Anxiety and Depression Scale [HADS]; Patient Health Questionnaire [PHQ]-9 & PHQ-2). Every patient participated in a gold-standard structured clinical interview (SCID) to assess depression. The diagnostic accuracy of the depression scales was assessed comparing a variety of scoring cut-points to the gold-standard diagnosis of depression. Potential effect modification was assessed using binomial regression models.

Results: The prevalence of current depression in this population, according to the gold standard, was 14.6%. The scale with the highest sensitivity (84.6%) was the HADS with a cut-point of six and the scale with the highest specificity (96.2%) was the PHQ-9 algorithm scoring method. Overall, the PHQ-9 at a cut-point of nine and the HADS at a cut-point of seven resulted in the greatest balance of sensitivity and specificity.

Conclusions: Appropriate scale cut-points should be chosen based on clinical or research goals and available resources. Disease-specific scale cut-points are recommended for future studies assessing depression in persons with epilepsy.
3.2 Introduction

Depression is often under recognized and improperly managed in persons with epilepsy, leading to reduced quality of life and compromised treatment outcomes [1]. A recent meta-analysis estimated the population-based prevalence of active depression in persons with epilepsy to be 23.1%, and persons with epilepsy had almost three times the odds of active depression relative to those without epilepsy [2]. In order to adequately identify depression in persons with epilepsy, screening tools are often recommended to rapidly detect cases of depression not previously diagnosed [3]. In 2009, the United States Preventive Service Task Force recommended screening for depression in locations where adequate resources exist [3]. The 2010 National Institute for Health and Clinical Excellence guidelines noted some concerns with routine depression screening, such as a high false-positive rate and the large number of resources required [4]. Screening for depression should be reserved for populations at high risk (such as those with epilepsy), where adequate treatment is available and resource-use is efficient [5].

Several studies have examined the properties of brief instruments for detecting depression in persons with epilepsy, using various reference standards and screening tools [6-9]. The Patient Health Questionnaire 9 (PHQ-9) is a commonly used tool for assessing depressive symptoms that allows for both categorical and dimensional scoring [10]. To our knowledge, the PHQ-9 has not been validated in persons with epilepsy. Further, semi-structured interviews such as the Mini International Neuropsychiatric Interview (MINI) are commonly employed to validate depression screening tools instead of the gold-standard Structured Clinical Interview for DSM-IV (SCID), as they are less resource-intensive [11]. However, the MINI is a brief interview originally designed for case-finding in primary care that is not considered a gold standard [12, 13]. A study validating the MINI against the SCID in persons with epilepsy reported only fair to
good agreement for all mood disorder modules [11]; imperfect agreement may lead to the improper categorization of persons with depression.

Most depression scales were developed for use in the primary care population [10, 14] and accepted cut-points need investigation in disease-specific settings. Research examining the performance of screening scales should not assume that general population cut-points are optimal for people with epilepsy. The purpose of this study was to validate a depression scale not previously validated in epilepsy (PHQ-9) and to assess new cut-points for scoring three depression rating scales compared to a gold standard depression diagnosis in persons with epilepsy. We examined whether disease-specific cut-points for each scale outperformed those recommended for the general population.

3.3 Methods

3.3.1 Participants

Participants were recruited consecutively from the only regional outpatient epilepsy clinic in Calgary (serving a population of more than 1,000,000) from August 2012 to January 2013. Patients were included if they spoke English fluently, had no hearing impairment and had no specialist diagnosed dementia, moderate or severe developmental delay, or aphasia. The study population was further restricted to those with a diagnosis of epilepsy based on evaluation by fellowship trained epileptologists and classified according to the new International League Against Epilepsy Commission on Classification and Terminology for organization of seizures and epilepsies[15]. The study protocol and consent forms were approved by the Conjoint Health Research Ethics Board of the University of Calgary.
3.3.2 Procedures

Participants were asked for their consent to complete a questionnaire, a telephone interview and a medical chart review. The questionnaire package included: a detailed socio-demographic section, three depression questionnaires (PHQ-9, PHQ-2 and Hospital Anxiety and Depression Scale [HADS]) and the Liverpool Adverse Event Profile (which measures adverse anti-epileptic medication effects). The telephone interview (SCID – see below) was conducted by trained senior graduate students blinded to depression status on questionnaires (agreement was excellent, \( \kappa = 1.00 \)) for all consenting participants within two weeks of their clinic appointment (to ensure the referenced time periods were consistent between all questionnaires and interviews). Following recruitment, the medical charts of all participants were reviewed to determine: epilepsy syndrome and seizure type; current anti-epileptic medications; current psychotropic medications and any additional non-pharmacological interventions for mental health conditions, such as being seen by a psychologist or a psychiatrist.

3.3.2.1 Measures

The PHQ-9 is a nine-item self-report instrument used to assess depressive symptoms, and can also be scored with an algorithm suggesting a diagnosis of depression. The items of the PHQ-9 map directly onto the DSM-IV criteria for major depression, including the criterion that symptoms be present more than half of the time for the previous two weeks (Appendix e-1). All items are scored from zero to three (e.g. zero indicates the problems did not bother the person at all while three indicated that they bothered them nearly every day). The PHQ-9 can be scored in two ways, the cut-point and algorithm methods. For the cut-point method, a total score of 10 or higher out of 27 is considered suggestive of major depression in the general population. For the algorithm method at least five symptoms must be endorsed more than half of the days, i.e. a
score of 2 or 3 (except suicide, where any score is counted), and one must be either depressed mood or loss of interest. The PHQ-2 includes only the two cardinal symptoms of depression (at least one of which must be present for the diagnostic criteria for a major depressive episode to be met), diminished interest or pleasure and depressed mood. The endorsement of one of these symptoms more than half of the days in a two-week period indicates the possibility of major depression. In the general population, the PHQ-9 cut-point method (10 out of 27) had a sensitivity of 88% and specificity of 88% when compared with a structured psychiatric interview [10].

The HADS is a 14-item self-report inventory for assessing symptoms of depression and anxiety (Appendix e-2)[14]. Each item is scored from 0-3, though the response choices differ for each question. In general practice the HADS with a cut-point of 8 resulted in a sensitivity of 89% and a specificity of 75% using patient visual analog scale ratings as the reference standard [14]. A recommended cut-point for the HADS in persons with epilepsy is 7 or 8 out of 21, though this study did not use a gold-standard measure to diagnose depression [16].

The SCID is widely considered to be the gold standard for the diagnosis of psychiatric conditions [11], as it was created to represent the DSM [17] criteria for mental disorders. The SCID is a semi-structured diagnostic interview that uses a trained health professional interviewer who is able to follow-up on the required symptoms and to explore areas that require clarification, making this kind of interview more flexible than fully structured diagnostic interviews. Depression was considered present if the diagnosis according to the SCID indicated the appropriate level of symptoms in the previous two weeks.
3.3.3 Statistical Analysis

Scores on all scales were analysed in a dichotomous manner, according to established and new (suggested by the study authors from past clinical experience) cut-points. Descriptive analyses were estimated by means and proportions and compared using t-tests, tests of proportions and analyses of variance. Measures of diagnostic accuracy [Sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV)] were calculated for all scales, using the SCID as the gold standard. Area under the receiver-operating characteristic curve (AUC) estimates were calculated, providing a measure of maximal Se versus Sp. Binomial regression was conducted to model depression status on each scale as a function of SCID status. The resulting coefficients represent the likelihood ratio positive, which is the probability of a positive test given depression according to the SCID over the probability of a positive test given no depression according to the SCID. Effect modification was explored using interaction terms. Variables considered potential effect modifiers or confounders were age, sex and self-report of medication side effects. All analyses were conducted in STATA 11.1 [18].

3.4 Results

The overall study had a total sample of 268 subjects (Figure 3.1). Nine hundred and twenty-five patients were initially seen in the epilepsy clinic during the data collection period. Five hundred fifteen participants were eligible, of which 445 were presented with the preliminary consent form. This was not possible for the other 70 because they were called into their clinic appointment before presentation was possible. Of those presented with the full consent (N=300), 89.3% (N=268) agreed to participate in the study.

The current analysis was restricted to the 185 persons with epilepsy who completed the SCID; no significant differences in socio-demographic and epilepsy-specific variables were
found between the full study group (N=300) and this sub-study sample (N=185). Baseline characteristics (socio-demographic and epilepsy-related variables) are listed in Table 3.1. Twenty-seven persons were found to be depressed according to the SCID, with an estimated prevalence of 14.6% (95% Confidence Interval (CI): 9.5-19.7). The prevalence of depression on the SCID was no different for women (13.7%, 95% CI: 6.7-20.7) than for men (15.6%, 95% CI: 8.0-23.1). Some characteristics were significantly different between those with and without depression, as captured by the SCID (Table 3.1): persons with depression were older at the time of first seizure, reported being smokers more often and reported more side effects from their anti-epileptic medication. Of all patients, 88.1% were currently taking anti-epileptic medications, with 38.4% reporting side effects from that medication based on self-report on a single yes/no question (separate from the Liverpool Adverse Event Profile).

Of those persons identified as depressed according to the SCID, 70% were not currently being treated for their depression according to our definition. More people were taking medication for their depression than receiving therapy (25.9% vs. 7.4%), while 7.9% were receiving both medication and therapy. The percentage of false negative results (cases missed by the scales) who were treated for depression ranged from 16.7% (PHQ-9 traditional cut-point) to 31.8% (PHQ-9 algorithm). Only 37% of persons who reported being depressed at any point in their life according to the SCID reported having been diagnosed by a health professional with depression. According to the SCID, 27.6% (95% CI: 21.1-34.1) of individuals had experienced a past major depressive episode. Of those people currently depressed on the SCID, 51.9% reported suicidal thoughts most days in the previous two weeks on the PHQ-9, while only 34.6% reported them during the SCID interview.
The Se, Sp, PPV and NPV for each depression scale and cut-point, compared with a SCID diagnosis of depression, are presented in Table 3.2. Maximum values of diagnostic accuracy (percent correctly classified, measured by the AUC) were achieved on different scales. Maximal sensitivity was achieved on the HADS using a cut-point of 6, specificity using the PHQ-9 algorithm method, PPV using the HADS traditional cut-point of 8 and NPV on both the PHQ-9 with a cut-point of 9 and the HADS with a cut-point of 6. Overall, the HADS with a cut-point of 7 (depression prevalence of 23.9%) and the PHQ-9 with a cut-point of 9 (depression prevalence of 26.6%) resulted in the greatest AUC (90.0% and 88.0%, respectively). The PHQ-2 resulted in an AUC of 75.2%, with a sensitivity of 42.3% and specificity of 87.3%.

Differences in scale performance by age and sex were examined using a binomial regression model for all scales reporting a dichotomous outcome. With the likelihood ratio positive as the effect measure, no effect measure modification by sex (p = .360) or age (p = .710) was detected for the PHQ-9 traditional cut-point (score of at least 10) scoring method (based on the sex or age by PHQ-9 score interaction term). Sex was not an effect modifier for the PHQ-9 algorithm scoring method (p = .916), nor was age (p = .928). When examining the PHQ-2, sex was found to be an effect modifier of the likelihood ratio positive (p = .047); the ratio of the probability of a participant with depression according to the SCID testing positive on the PHQ-2 relative to the probability of a participant without depression according to the SCID testing positive on the PHQ-2 (the likelihood ratio positive) is lower among women than it is for men. Age was not an effect modifier for the PHQ-2 (p = .884). For the HADS traditional cut-point (score of at least 8), neither sex (p = .142) nor age (p = .777) were effect modifiers of the likelihood ratio positive. Effect modification also assessed for all scales according to medication side effects, where no differences were found.
3.5 Conclusion

The optimal tool to screen for depression in persons with epilepsy depends on several factors, including the goals of the assessment, clinical and health care needs, and properties of the measurement scale. If the goal of a study is to maximize sensitivity (as may be the case in a resource-rich clinical environment where false negatives are a major concern, but false positives are a lesser concern), the ideal tool among the options examined here would be the HADS with a cut-point of six. For avoiding false positives (as may be preferred in an environment where mental health resources are more scarce or concerns exist related to incorrectly diagnosing and treating patients with depression), the best tool among those examined was found to be the PHQ-9, using the algorithm scoring method. However, the algorithm scoring recommended for the general population tended to be insensitive in those with epilepsy. Overall, traditional cut-points resulted in moderate sensitivities and specificities whereas newly suggested scoring cut-points fared far better. The greatest balance of sensitivity and specificity was achieved on the PHQ-9 with a cut-point of nine and the HADS with a cut-point of seven. We also found no effect of including self-reported medication side effects in the model, a common critique of general versus disease-specific depression scales. It is possible, however, that side effects experienced by the participants were not attributed to their epilepsy medication. Almost 70% of those persons missed by the screening tools (false negatives) were not being treated for depression. The optimal tool for screening depends on many different factors, including acceptability and cost; in a resource-scarce environment where the goal is to minimize false positive results, the tool with the highest specificity may be preferred. If this choice is made, clinicians would need to remain vigilant to depressive symptoms since they could not assume that the screening instrument would detect a high proportion of cases.
The relatively high prevalence of depression in epilepsy has garnered much attention in recent years. The estimate of current depression in the present study (14.6%) is very similar to that reported in a recent study of almost 4000 persons with epilepsy (17.5%) [19]. The assessment and management of depression in persons with epilepsy was identified as a priority in a clinical practice statement from the Commission on the Neuropsychiatric Aspects of Epilepsy [20]. The Commission [20] recommends screening with the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) or the PHQ-2 for all new persons with epilepsy, and at least annually in all other patients (the current study was designed before these recommendations were published). A previous study found high PPV and Se for the PHQ-2 (100% and 80%, respectively) in persons with epilepsy using the MINI as the reference standard. The current study, however, using a gold standard diagnosis of depression, found a PPV of 35.5% and Se of 42.3% using the PHQ-2. Measures of diagnostic accuracy this low would result in high false positive and false negative rates, leading to inappropriate resource utilization and perhaps sub-optimal treatment of presumed depression [21].

Disease-specific cut-points on general scales resulted in sensitivity and specificity estimates similar to those achieved using disease-specific scales [7, 8]. The HADS and the PHQ-9 performed comparably in this study, and the appropriate cut-point should be selected based on the locally appropriate trade-off between sensitivity and specificity. Scales may not need to be specific to a condition, but rather the cut-points used should be adapted to reflect differences in depression symptom presentation (i.e., have a lower threshold for diagnosing depression in these populations). Investigating a variety of scale cut-points in this manner is an exploratory methodology that should be replicated to strengthen the evidence about the performance of these scales using different cut-points.
The current study used a consecutive sample of persons with clinician-diagnosed epilepsy and employed a scale that was not previously validated, a definite strength. These participants were not new consultations, but rather were followed by the physicians. Most importantly, it used the SCID mood disorder module to diagnose depression in this population. New cut-points were explored, for a total of nine validated scoring methods, along with potentially extraneous sex and age effects. Interestingly, the cut-points traditionally suggested for use in the general population do not have the same applicability in this population with epilepsy. It will be very important to replicate this study, as it is clear that many people with depression are not diagnosed and as such, not treated. The study is not without limitations. Our sub-sample from those presenting to a tertiary care center could reflect a more severe sample of persons with epilepsy compared to the general population. The small sample size in some subgroups may have resulted in insufficient power to detect significant differences or effect modification. Some between-group differences between those depressed and not depressed appear to be clinically important, though did not achieve statistical significance because of small cell sizes. It should be noted that the PHQ-9 is freely available in the public domain, whereas the HADS requires licensing and payment. Finally, a disease-specific depression scale was not directly compared to general depression scales in this study.

Screening for depression in epilepsy can be an effective method to recognize previously unidentified cases of depression. Various scales for assessing depression in epilepsy have been validated, and it appears that using appropriate cut-points for the setting is more important than the content of the scale. Both the PHQ-9 and HADS are appropriate for use in the epilepsy population. The timely identification of depression in persons with epilepsy is important, as is proper management after diagnosis.
3.6 References


18. *STATA*. 2013, STATA Corp.: College Station, TX.


Figure 3.1. Study Flow Diagram of Patients Seen between August 2012 and January 2013

All Patients Seen in the Epilepsy Clinic

N = 892

Ineligible
N = 377

Outside Calgary
N = 229

Not Fluent in English
N = 22

Dementia, delay &/or aphasia
N = 126

Eligible
N = 515

Presented with Preliminary Consent
N = 445

Not Presented with Preliminary Consent
N = 70

Yes and Presented with Full Consent
N = 300

No
N = 123

Not Presented with Full Consent
N = 22

Yes
N = 268

No
N = 32

Yes to SCID
N = 185

No to SCID
N = 83
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=185)</th>
<th>With Depression (N=27)</th>
<th>Without Depression (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (range)</td>
<td>40.3 (18.2-78.1)</td>
<td>39.2 (21.0-66.8)</td>
<td>40.5 (18.2-78.1)</td>
</tr>
<tr>
<td>Mean age of seizure onset (years) (range)</td>
<td>23.4 (0-76.3)</td>
<td>31.9 (1.9-76.3)</td>
<td>21.9 (0-74.1)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>51.4</td>
<td>48.2</td>
<td>51.9</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Common law (%)</td>
<td>55.1</td>
<td>40.7</td>
<td>57.6</td>
</tr>
<tr>
<td>Widowed/Separated/Divorced (%)</td>
<td>10.8</td>
<td>11.1</td>
<td>10.8</td>
</tr>
<tr>
<td>Single/Never married (%)</td>
<td>34.1</td>
<td>48.2</td>
<td>31.7</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High school or less</td>
<td>60.5</td>
<td>74.1</td>
<td>58.2</td>
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<tr>
<td>Greater than high school</td>
<td>39.5</td>
<td>25.9</td>
<td>41.8</td>
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<tr>
<td>Working at a paid job (%)</td>
<td>66.5</td>
<td>55.6</td>
<td>68.4</td>
</tr>
<tr>
<td>Currently drinks alcohol (%)</td>
<td>63.2</td>
<td>77.8</td>
<td>61.2</td>
</tr>
<tr>
<td>Currently smokes cigarettes (%)</td>
<td>19.5</td>
<td>40.7</td>
<td>15.8</td>
</tr>
<tr>
<td>Currently use illegal drugs (%)</td>
<td>15.7</td>
<td>25.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Epilepsy type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal epilepsy (%)</td>
<td>64.3</td>
<td>69.2</td>
<td>63.5</td>
</tr>
<tr>
<td>Generalized epilepsy (%)</td>
<td>26.4</td>
<td>23.1</td>
<td>26.9</td>
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<tr>
<td>Unknown epilepsy (%)</td>
<td>9.3</td>
<td>7.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Epilepsy Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic (%)</td>
<td>26.9</td>
<td>23.1</td>
<td>27.6</td>
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<tr>
<td>Structural/Metabolic (%)</td>
<td>35.7</td>
<td>30.8</td>
<td>36.5</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>37.4</td>
<td>46.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Mean Physical Quality of Life (range)^b</td>
<td>48.1</td>
<td>48.7</td>
<td>47.9</td>
</tr>
<tr>
<td>Mean Mental Quality of Life (range)^b</td>
<td>35.5</td>
<td>27.7</td>
<td>37.3</td>
</tr>
<tr>
<td>Currently not being treated for depression (%)$</td>
<td>73.5</td>
<td>70.3</td>
<td>74.1</td>
</tr>
<tr>
<td>Currently taking psychotropic medication (%)$</td>
<td>19.7</td>
<td>25.9</td>
<td>20.9</td>
</tr>
<tr>
<td>Currently receiving therapy for depression (%)$</td>
<td>12.3</td>
<td>12.0</td>
<td>22.2</td>
</tr>
<tr>
<td>Self-report of epilepsy medication side effects (%)*</td>
<td>38.4</td>
<td>55.6</td>
<td>35.4</td>
</tr>
<tr>
<td>Self-report of depression diagnosis (%)¶</td>
<td>24.7</td>
<td>30.8</td>
<td>24.5</td>
</tr>
<tr>
<td>Self-report of suicidal thoughts or ideation (%)^</td>
<td>12.4</td>
<td>51.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Self-report of epilepsy disease severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate-Not severe (%)</td>
<td>90.5</td>
<td>88.9</td>
<td>90.8</td>
</tr>
<tr>
<td>Very-Extremely severe (%)</td>
<td>9.5</td>
<td>11.1</td>
<td>9.2</td>
</tr>
<tr>
<td>Self-report of disabling seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately-Not disabling (%)</td>
<td>76.9</td>
<td>66.7</td>
<td>78.4</td>
</tr>
<tr>
<td>Very-Extremely disabling (%)</td>
<td>23.1</td>
<td>33.3</td>
<td>21.6</td>
</tr>
</tbody>
</table>

a With/without depression defined as current depressive episode on clinical (SCID) interview
b Quality of Life based on Short Form 12 scores. Higher scores indicate greater quality of life
$ Based on medical chart review and patient self-report of medication or therapy
* Defined as self-reported medication side effects (yes or no)
¶ Defined as self-reported depression diagnosis by a health professional (yes or no)
^ Defined as item nine on the Patient Health Questionnaire Scale
**Bold-faced type** = significantly different at p=.05
*Italicized type* = significantly different at p=.10
Table 3.2. Estimated Prevalence of Depression and Associated Measures of Diagnostic Accuracy for Nine Different Scoring Methods of Depression Screening Tools among Persons with Epilepsy (n=185)

<table>
<thead>
<tr>
<th>Questionnaire (cut-point score)</th>
<th>Depression Prevalence (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>Positive Predictive Value (%) (95% CI)</th>
<th>Negative Predictive Value (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 Cut-point (9)</td>
<td>26.6</td>
<td>82.61 (61.22-95.05)</td>
<td>82.19 (75.01-88.02)</td>
<td>42.22 (27.66-57.85)</td>
<td>96.77 (91.95-99.11)</td>
</tr>
<tr>
<td>PHQ-9 Traditional Cut-point (10)</td>
<td>21.9</td>
<td>73.91 (51.59-89.77)</td>
<td>86.30 (79.64-91.43)</td>
<td>45.95 (29.49-63.08)</td>
<td>95.45 (90.37-98.31)</td>
</tr>
<tr>
<td>PHQ-9 Cut-point (11)</td>
<td>18.3</td>
<td>60.87 (38.54-80.29)</td>
<td>88.36 (82.01-93.07)</td>
<td>45.16 (27.32-63.97)</td>
<td>93.48 (87.98-96.97)</td>
</tr>
<tr>
<td>PHQ-9 Cut-point (12)</td>
<td>14.8</td>
<td>52.17 (30.59-73.18)</td>
<td>91.10 (85.26-95.17)</td>
<td>48.00 (27.80-68.69)</td>
<td>92.36 (86.74-96.13)</td>
</tr>
<tr>
<td>PHQ-9 Algorithm</td>
<td>5.9</td>
<td>18.52 (6.30-38.08)</td>
<td>96.20 (91.92-98.59)</td>
<td>45.45 (16.75-76.62)</td>
<td>87.36 (81.49-91.90)</td>
</tr>
<tr>
<td>PHQ-2 Cut-point (2)</td>
<td>16.9</td>
<td>42.31 (23.35-63.08)</td>
<td>87.26 (81.01-92.04)</td>
<td>35.48 (19.23-54.63)</td>
<td>90.13 (84.25-94.37)</td>
</tr>
<tr>
<td>HADS Cut-point (6)</td>
<td>31.1</td>
<td>84.62 (65.13-95.64)</td>
<td>77.92 (70.54-84.20)</td>
<td>39.29 (26.50-53.25)</td>
<td>96.77 (91.95-99.11)</td>
</tr>
<tr>
<td>HADS Cut-point (7)</td>
<td>23.9</td>
<td>80.77 (60.65-93.45)</td>
<td>85.71 (79.17-90.83)</td>
<td>48.84 (33.31-64.54)</td>
<td>96.35 (91.69-98.80)</td>
</tr>
<tr>
<td>HADS Traditional Cut-point (8)</td>
<td>17.2</td>
<td>69.23 (48.21-85.67)</td>
<td>91.56 (86.00-95.43)</td>
<td>58.06 (39.08-75.45)</td>
<td>94.63 (89.69-97.65)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Note: bolded entries represent the largest value in that column
<sup>a</sup>As diagnosed by the Structured Clinical Interview for DSM-IV
PHQ: Patient Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; 95% CI: 95% Confidence Interval
Appendix 1. Patient Health Questionnaire-9 Items

Over the last 2 weeks, how often have you been bothered by any of the following problems?
1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself- or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed. Or, being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or of hurting yourself in some way
Appendix 2. Hospital Anxiety and Depression Scale Depression Items

1. I still enjoy the things I used to enjoy
2. I can laugh and see the funny side of things
3. I feel cheerful
4. I feel as if I am slowed down
5. I have lost interest in my appearance
6. I look forward with enjoyment to things
7. I can enjoy a good book or radio or TV programme
CHAPTER 4: PATTERNS AND FREQUENCY OF THE TREATMENT OF DEPRESSION IN PERSONS WITH EPILEPSY
4.1 Abstract

**Objective:** Though the prevalence of depression in epilepsy is high, most persons with epilepsy (PWE) with comorbid depression often remain untreated. The current study aims to determine the proportion of PWE receiving depression-related treatment and to characterize the type of treatment received.

**Methods:** Persons with epilepsy (n=185) from the only epilepsy clinic in a large urban city completed questionnaires and a gold-standard structured clinical interview (SCID) to assess current and past depression. Treatment for depression was ascertained through patient self-report (of pharmacological or non-pharmacological management) and a medical chart review (of pharmacological or non-pharmacological management).

**Results:** Of those with depression (n=27), the majority (70.3%) were not on any depression-related treatment. In persons with current depression, non-pharmacological management was the most common treatment method, followed by treatment with psychotropic medications such as selective serotonin reuptake inhibitors. More individuals with a past history of depression (n=43) were treated (37.2%); it was more common for these individuals to be treated with pharmacological measures.

**Conclusions:** In this population of persons with epilepsy, the proportion of people treated for current depression was very low. Future studies should investigate barriers to treatment and how depression treatment can be optimized for persons with epilepsy.
4.2 Introduction

Depression is common in persons with epilepsy, with a reported prevalence in the general population of 23.1%[1]. Depression continues to be under-recognized and improperly managed in PWE, despite its high prevalence[2]. About half of persons with epilepsy with comorbid depression are treated, though estimates vary from 17-60%[3, 4]. These studies, however, did not assess both pharmacological and non-pharmacological treatments for depression or use a gold standard to diagnose depression.

Depression and epilepsy alone are risk factors for suicide[5] and clinicians may be wary of introducing additional medications that may further increase this risk[6]. Reasons for the reluctance by many physicians to treat depression in epilepsy could be the misconception that all anti-depressants reduce the seizure threshold or enhance anti-epileptic drug (AED) side effects[2, 6].

A variety of pharmacological and non-pharmacological treatments have been shown to be effective and promising options for treating depression in persons with epilepsy. Anti-depressants are usually considered a first-line pharmacological treatment for depression in epilepsy, taking into account the current AED regimen[7]. Overall, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with low rates of seizures in persons with epilepsy and in some cases may even increase the seizure threshold[8]. Non-pharmacological treatments for depression in persons with epilepsy have also been explored primarily in an attempt to avoid negative AED side effects[9-12]. Transcranial magnetic stimulation (TMS)[11] and vagus nerve stimulation (VNS)[10] have been employed in treating depression in persons with epilepsy, but with mixed effects[13]. Despite their potential
as treatment methods for depression in persons with epilepsy, they still require further testing in large trials to ensure their effectiveness.

Cognitive, behavioral, and interpersonal therapies have also been shown to improve depressive symptoms in persons with epilepsy in a number of randomized controlled trials [14, 15]. A cognitive-behavioural therapy (CBT) program, Project UPLIFT (Using Practice and Learning to Increase Favorable Thoughts) was developed to help reduce the symptoms of depression in persons with epilepsy [12] and the PEARLS (Program to Encourage Active, Rewarding Lives for Seniors) randomized controlled trial focused on counselling, problem solving and behavioural activation for depression in persons with epilepsy [9].

Pharmacological management is the major method for treating depression in persons with epilepsy. Non-pharmacological treatments and psychological therapies such as TMS, VNS and CBT also show promising effects. Existing literature on the prevalence of treated depression in PWE does not use gold-standard tools to diagnose depression and commonly focuses on pharmacological therapies. Treatment for depression may vary depending on access to resources, and it is important to examine this question in a Canadian context where access is universal. The purpose of the current study is to: (1) determine the proportion of persons with epilepsy with depression (diagnosed according to a gold-standard) who are receiving pharmacological and/or non-pharmacological treatments for depression; and (2) assess the type of treatment received.

4.3 Methods

4.3.1 Participants

Participants were recruited consecutively from the only regional outpatient epilepsy clinic in Calgary (serving a population of more than 1,000,000) from August 2012 to January 2013. Patient were included if they spoke English fluently, had no hearing impairment (for later phone
interview) and had no specialist-diagnosed dementia, moderate or severe developmental delay, or aphasia. The study population was further restricted to those with a diagnosis of epilepsy based on evaluation by fellowship trained epileptologists and classified according to the new International League Against Epilepsy Commission on Classification and Terminology for organization of seizures and epilepsies[16]. The study protocol and consent forms were approved by the Conjoint Health Research Ethics Board.

4.3.2 Procedures

Participants were asked to consent to completing a questionnaire and telephone interview. The questionnaire package included: a detailed socio-demographic section, three depression questionnaires (PHQ-9[17], PHQ-2 and Hospital Anxiety and Depression Scale [HADS][18]), a quality of life questionnaire (Short Form (SF) -12[19]) and the Liverpool Adverse Event Profile[20] (which measures adverse anti-epileptic medication effects). Also included in the questionnaire package were questions related to the diagnosis and treatment of depression. Participants were asked if they had ever been diagnosed with depression by a health professional, whether they were currently on medication for depression and whether they were receiving non-pharmacological treatment for depression (and from who). The telephone interview (SCID – see below) was conducted by trained senior clinical psychology graduate students blinded to depression status on questionnaires (agreement was perfect, κ= 1.00) for all consenting participants within two weeks of their clinic appointment (to ensure the referenced time periods were consistent between all questionnaires and interviews). Following recruitment, the medical charts of all participants were reviewed to determine: epilepsy syndrome and seizure type; current anti-epileptic medications; current psychotropic medications; and, any additional non-
pharmacological interventions for mental health conditions, such as being seen by a psychologist or psychiatrist.

4.3.2.1 Measures

The SCID is widely considered to be the gold standard for the diagnosis of psychiatric conditions, as it was created to represent the DSM-IV[21] criteria for mental disorders. The SCID is a semi-structured diagnostic interview that uses a trained health professional interviewer who is able to follow-up on the required symptoms and to explore areas that require clarification, making this kind of interview more flexible than fully structured diagnostic interviews, which is expected to lead to increased accuracy. Depression was considered present if the diagnosis according to the SCID indicated the appropriate level of symptoms in the previous two weeks.

The treatment of depression was defined using two data sources: medical chart review and patient self-report. If the patient’s medical chart reported the use of psychotropic medication for any indication (as the positive psychotropic effects of the medication may occur regardless of the reason for prescription), or non-pharmacological treatment for depression of any kind, a person was considered treated. In addition, if the participant indicated currently taking a medication for depression, or was being seen by a psychologist, counsellor or therapist for depression they were considered treated. The appropriateness and level of treatment were not assessed.

Using an algorithm created by Beck and Patten, the proportion of depressed persons who were receiving treatment for depression was adjusted for the possibility of successful treatment in other persons with depression[22]. Adjusting the treated proportion of depression for successful treatment outcomes will provide an estimate of depression treatment that accounts for
persons without active depression who are treated. The “liberal adjusted” method will be used to calculate the adjusted proportion of treatment \((P)\).

\[
P = \frac{(a + c)}{(a + b + c)}
\]

Where \(a\) is the number of subjects with depression taking antidepressants, \(b\) is the number of subjects with depression not taking antidepressants and \(c\) is the number of subjects without depression taking antidepressants.

4.3.3 Statistical Analysis

Statistical analysis was performed using STATA version 11.0[23]. Basic descriptive statistics were calculated and compared using t-tests and exact tests of proportions. The accepted level of significance for all p-values in this study is \(\alpha < .05\).

4.4 Results

The overall study had a total sample of 268 subjects (Figure 4.1). Nine hundred and twenty-five patients were initially seen in the epilepsy clinic during the data collection period. Five hundred fifteen participants were eligible, of which 445 were presented with the preliminary consent form. This was not possible for the other 70 because they were called into their clinic appointment before presentation was possible. Of those presented with the full consent (\(N=300\)), 89.3% (\(N=268\)) agreed to participate in the study.

The current analysis was restricted to the 185 persons with epilepsy who completed the SCID; no significant differences in socio-demographic and epilepsy-specific variables were found between the full study group and this sub-study sample. Baseline characteristics (socio-demographic and epilepsy-related variables) are listed in Table 4.1. Twenty-seven persons were found to be currently depressed according to the SCID, with an estimated prevalence of 14.6% (95% Confidence Interval (CI): 9.5-19.7). The prevalence of depression on the SCID was no
different for women 13.7% (95% CI: 6.7-20.7) than for men (15.6% (95% CI: 8.0-23.1). Some characteristics were significantly different between those with and without depression, as captured by the SCID (Table 4.1): persons with depression were older at the time of first seizure, reported being smokers more often and reported more side effects from their anti-epileptic medication. The most commonly reported AED side effects were tiredness (60.3%), problems with memory (55.4%) and difficulties sleeping (52.2%). No participants in the study were receiving stimulation therapy (VNS, TMS, Deep Brain Stimulation (DBS)) for their depression or epilepsy.

Of those persons diagnosed with depression, 70.3% were not receiving any depression-related therapies (n=19). There was no difference in the proportion of men and women being treated for their depression (p=.475). In persons receiving treatment for their depression (n=8), most (50%) were receiving non-pharmacological treatment alone, 25% of persons were only on medication (n=2) and 25% were receiving both pharmacological and non-pharmacological treatment (n=2). Those being treated with medication (n=4) were on at least one SSRI, including citalopram, escitalopram and sertraline (Table 4.2). Other medications included trazadone, quetiapine and mirtazapine, which were being taken by individuals on at least one other psychotropic medication. Though seven people reported currently taking medications for their depression, only four individuals had this recorded in their medical chart. Of the individuals receiving non-pharmacological treatment (n=6), most reported receiving it from their family doctor (n=2), followed by a psychologist (n=1), counsellor (n=1), psychiatrist (n=1) and other specialist (n=1). Using the Beck and Patten method[22], the adjusted proportion of persons with depression receiving treatment was 53.1%. The treated prevalence of depression according to
various cut-point scores on three depression questionnaires (PHQ-9, PHQ-2, HADS) is reported in Table 4.3.

A past history of depression was reported in 27.2% (n=43) of participants (those without a current depressive episode) and of those, 16 were receiving treatment (37.2%). The majority (n=12) were on medication alone, three were receiving only non-pharmacological treatment and one individual was receiving both pharmacological and non-pharmacological treatment. Most (61.5%) individuals were on one psychotropic medication (n=8) and the remainder (n=5) were on two psychotropic medications. The most common psychotropic medications were atypical antipsychotics (n=7) (aripiprazole, risperidone, quetiapine) and SSRIs (n=7) (citalopram, escitalopram, paroxetine, fluoxetine). Other medications included mood stabilizers, benzodiazepines and SNRIs (all indicated for psychiatric reasons).

The most common AEDs (Table 4.4) in persons currently being treated for their depression were clobazam (n=3), phenytoin (n=2), clonazepam (n=2), lamotrigine (n=2), and topiramate (n=2). Most participants being treated for their depression were on polytherapy (85.7%). Of those persons with epilepsy who were depressed in the past, but not currently depressed, the most common AEDs were lamotrigine (n=7), sodium valproate (n=4) and lorazepam (n=3).

4.5 Discussion

Despite the high prevalence of depression in persons with epilepsy, most currently depressed individuals remain untreated. In those persons with epilepsy currently depressed according to a gold-standard clinical interview, only 30% were receiving either pharmacological or non-pharmacological therapies that are used to treat depression. A slightly higher proportion of individuals (37.2%) with a past history of major depression were receiving treatment. Most
persons with epilepsy with current depression were receiving non-pharmacological treatment, whereas most people receiving treatment for past depression were on pharmacological therapies. The most commonly used medications in persons being treated for depression were SSRIs and most individuals reported receiving non-pharmacological treatment from their family doctor.

The prevalence of treated depression in the current study (30%) is consistent with estimates from previous studies on depression in persons with epilepsy; a study of depressed PWE found that only 17% of these individuals were on antidepressants[4], while another study reported that almost 60% of currently depressed persons with epilepsy were treated with medication[3]. After adjusting for those persons being successfully treated for depression[22], the prevalence of treatment increased to 53.1%. Since health care is universal in the recruitment setting, it is possible that barriers to treatment are not financial; potential barriers could be stigma, prescriber fears, or lack of adherence. These estimates are quite variable, which could be due to different study populations, methods of diagnosing depression and how treatment was defined. The relative dearth of information on this topic highlights the importance of identifying persons with epilepsy with depression and ensuring their symptoms are properly treated.

The high frequency of atypical antipsychotic use (43.8% in persons with a past history of depression) in this study is notable. Atypical antipsychotics are increasingly being prescribed for non-psychotic conditions, such as sleep difficulties and anxiety disorders[24]. Atypical antipsychotic use increased by 25% in a Canadian province between 1992 and 1998, largely due to an increase in the number of available drugs[25]. A recent systematic review of antipsychotic prescribing trends noted the potential harm in the widespread use of these medications, given their numerous metabolic side effects[24]- weight gain and glucose dysregulation are common side effects of these medications[26].
To date, only one randomized controlled trial has been published on the use of pharmacotherapy to treat depression in persons with epilepsy [27]. This study, published in 1985[28], assessed the effect of a tricyclic antidepressant (TCA) (amitriptyline) and a second-generation norepinephrine-dopamine reuptake inhibitor (NDRI) (nomifensine) versus placebo. At six weeks follow-up, all treated patients showed reduced depression scores; at 12 weeks follow-up nomifensine was superior in reducing depressive symptoms relative to amitriptyline[28]. It should be noted that nomifensine was withdrawn from market in 1986 following numerous reports of haemolytic anemia[29]. Since that time, newer antidepressant drugs have been developed (SSRIs, SNRIs) and are now recommended as the first-line pharmacological treatment of depression in persons with epilepsy [30], though no randomized controlled trials of their effectiveness have been published.

Trials investigating the use of cognitive behavioural therapy and counselling for depression in PWE have been conducted[9, 12]. Project UPLIFT used mindfulness-based cognitive therapy to treat depression in an eight-week trial and found that depressive symptoms decreased more in the intervention group than the waitlist group over eight weeks follow up[12]. The PEARLS trial used problem-solving, behavioural activation and psychiatric consultation; in a period of 12 months, persons with epilepsy randomized to the intervention reported less severe depression and lower suicidal ideation than those in the usual care group[9]. This effect was maintained, though attenuated, at 18 months[31]. These interventions appear to reduce depressive symptoms in persons with epilepsy, though their effectiveness in the long-term has not been explored. In addition, pharmacotherapy and counselling have not been directly compared as treatments in a randomized controlled trial for depression in persons with epilepsy. There is a possibility that the combination of pharmacological and non-pharmacological
treatments for depression may confer added benefits to persons with epilepsy than either
treatment alone, as seen in persons with only depression [32, 33].

Depression may go untreated in persons with epilepsy because of fear of increasing the
risk of suicidal thoughts, attempts and completions[34]. A report published by the Food and
Drug Administration (FDA) in 2008 prompted the inclusion of a black box warning for all AEDs
of the increased risk of suicide[35]. Since the publication of the FDA meta-analysis, numerous
high-quality population-based reports have been published contradicting its findings. In a study
of over five million patients, AEDs were not associated with an increased risk of suicidal events
in persons with epilepsy (in fact a small protective effect was found)[36]. Another reason
depression may go untreated in persons with epilepsy is related to the possibility of anti-
depressants lowering the seizure threshold[37]. Newer antidepressants, such as SSRIs and
SNRIs, have a relatively low risk of inducing seizures and are recommended for treating
depression in PWE; clomipramine and bupropion should be avoided as pro-convulsive properties
may exist[37]. Reluctance may also exist in treating depression in epilepsy because of the
potential of enhancing adverse AED effects, such as weight gain, worsening of sexual side
effects and decreased bone mineral density[38]. Potential interactions between psychotropic and
AEDs should be considered on a case-by-case basis and it is suggested that these medications be
initiated at the lowest possible therapeutic dose[8].

The current study used a consecutive sample of persons with clinician-diagnosed epilepsy
and the SCID mood disorder module to diagnose depression. It not only looked at medications,
but also non-pharmacological therapies to determine the proportion receiving depression-related
treatment. The study is not without limitations. Our sub-sample from those presenting to a
tertiary care center could reflect a more severe sample of persons with epilepsy compared to the
general population. The small sample size in the subgroup of those with treated depression may have resulted in insufficient power to detect significant differences. We were unable to assess the dosage and appropriateness of the prescribed medications for depression. The definition of non-pharmacological treatment in this study was very inclusive, and may not include strictly evidence-based treatments. Overall, the definition of treatment was very broad and may include persons receiving treatment for another indication; the treated prevalence of depression in this sample of persons with epilepsy is likely an overestimate.

Though many evidence-based treatments exist, the majority of persons with epilepsy with current depression remain untreated. It is important to explore barriers to treatment in this population so they can be addressed both with patients and care providers. In addition, clinical care pathways should be examined going forward, as resources may be limited in some settings: cost-effective and easily accessible therapies will be essential. Patterns of atypical antipsychotic use in persons with epilepsy should be further explored. A randomized controlled trial of newer anti-depressants to treat depression in epilepsy is necessary, as is a comparison between the effectiveness of pharmacological and non-pharmacological treatments. Until that time, it is important to identify persons with epilepsy with depression and pursue appropriate treatment options.

4.6 References


23. StataCorp, *STATA*. 2009: College Station, TX.


Figure 4.1. Study Flow Diagram of Patients Seen between August 2012 and January 2013

All Patients Seen in the Epilepsy Clinic
N = 892

Ineligible
N = 377
- Outside Calgary
  N = 229
- Not Fluent in English
  N = 22
- Dementia, delay &/or aphasia
  N = 126

Eligible
N = 515
- Presented with Preliminary Consent
  N = 445
- Present with Preliminary Consent
  N = 70

Yes and Presented with Full Consent
N = 300
- Yes
  N = 268
  - Yes to SCID
    N = 185
  - No to SCID
    N = 83
- No
  N = 123

Not Presented with Full Consent
N = 22
Table 4.1. Characteristics of Persons with Epilepsy Overall and by Depression Status\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=185)</th>
<th>With Depression (N=27)(^a)</th>
<th>Without Depression (N=158)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (range)</td>
<td>40.3 (18.2-78.1)</td>
<td>39.2 (21.0-66.8)</td>
<td>40.5 (18.2-78.1)</td>
</tr>
<tr>
<td>Mean age of seizure onset (years) (range)</td>
<td>23.4 (0-76.3)</td>
<td>31.9 (1.9-76.3)</td>
<td>21.9 (0-74.1)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>51.4</td>
<td>48.2</td>
<td>51.9</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Common law (%)</td>
<td>55.1</td>
<td>40.7</td>
<td>57.6</td>
</tr>
<tr>
<td>Widowed/Separated/Divorced (%)</td>
<td>10.8</td>
<td>11.1</td>
<td>10.8</td>
</tr>
<tr>
<td>Single/ Never married (%)</td>
<td>34.1</td>
<td>48.2</td>
<td>31.7</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>60.5</td>
<td>74.1</td>
<td>58.2</td>
</tr>
<tr>
<td>Greater than high school</td>
<td>39.5</td>
<td>25.9</td>
<td>41.8</td>
</tr>
<tr>
<td>Working at a paid job (%)</td>
<td>66.5</td>
<td>55.6</td>
<td>68.4</td>
</tr>
<tr>
<td>Currently drinks alcohol (%)</td>
<td>63.2</td>
<td>77.8</td>
<td>61.2</td>
</tr>
<tr>
<td>Currently smokes cigarettes (%)</td>
<td>19.5</td>
<td>40.7</td>
<td>15.8</td>
</tr>
<tr>
<td>Currently use illegal drugs (%)</td>
<td>15.7</td>
<td>25.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Epilepsy type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal epilepsy (%)</td>
<td>64.3</td>
<td>69.2</td>
<td>63.5</td>
</tr>
<tr>
<td>Generalized epilepsy (%)</td>
<td>26.4</td>
<td>23.1</td>
<td>26.9</td>
</tr>
<tr>
<td>Unknown epilepsy (%)</td>
<td>9.3</td>
<td>7.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Epilepsy Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic (%)</td>
<td>26.9</td>
<td>23.1</td>
<td>27.6</td>
</tr>
<tr>
<td>Structural/Metabolic (%)</td>
<td>35.7</td>
<td>30.8</td>
<td>36.5</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>37.4</td>
<td>46.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Mean Physical Quality of Life (range)(^b)</td>
<td>48.1</td>
<td>48.7</td>
<td>47.9</td>
</tr>
<tr>
<td>Mean Mental Quality of Life (range)(^b)</td>
<td>35.5</td>
<td>27.7</td>
<td>37.3</td>
</tr>
<tr>
<td>Self-report of epilepsy disease severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate-Not severe (%)</td>
<td>90.5</td>
<td>88.9</td>
<td>90.8</td>
</tr>
<tr>
<td>Very-Extremely severe (%)</td>
<td>9.5</td>
<td>11.1</td>
<td>9.2</td>
</tr>
<tr>
<td>Self-report of disabling seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately-Not disabling (%)</td>
<td>76.9</td>
<td>66.7</td>
<td>78.4</td>
</tr>
<tr>
<td>Very-Extremely disabling (%)</td>
<td>23.1</td>
<td>33.3</td>
<td>21.6</td>
</tr>
</tbody>
</table>

\(^a\) With/without depression defined as current depressive episode on clinical (SCID) interview

\(^b\) Quality of Life based on Short Form 12 scores. Higher scores indicate greater quality of life

**BOLD**-faced type indicates a significant difference at p<.05
<table>
<thead>
<tr>
<th>Medication Classification</th>
<th>Generic Medication Names (Examples)</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine Oxidase Inhibitors</td>
<td>Isocarboxazid, Phenelzine</td>
<td>Inhibit the activity of the monoamine oxidase enzyme, preventing the breakdown of monoamine neurotransmitters</td>
</tr>
<tr>
<td>Tricyclic Antidepressant</td>
<td>Amitryptiline, Nortriptyline, Clomipramine</td>
<td>Blocks the serotonin transporter and norepinephrine transporter, leading to an elevation of the neurotransmitters in the synapse</td>
</tr>
<tr>
<td>Selective Serotonin Reuptake Inhibitor</td>
<td>Citalopram, Escitalopram, Sertraline, Paroxetine, Fluoxetine</td>
<td>Inhibits the reuptake of serotonin into the presynaptic cell, increasing the amount of serotonin available to bind to the postsynaptic receptor</td>
</tr>
<tr>
<td>Serotonin Norepinephrine Reuptake Inhibitor</td>
<td>Duloxetine, Venlafaxine</td>
<td>Inhibits the reuptake of serotonin and norepinephrine into the presynaptic cell, increasing the amount of serotonin and norepinephrine available to bind to the postsynaptic receptor</td>
</tr>
<tr>
<td>Atypical Antidepressant</td>
<td>Buproprion</td>
<td>Acts as a mild dopamine reuptake inhibitor, a weak norepinephrine reuptake inhibitor and a nicotinic acetylcholine receptor antagonist</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Zopiclone, Lorazepam, Clonazepam, Diazepam</td>
<td>Enhance the effect of gamma-aminobutyric acid (GABA) at the GABA-A receptor</td>
</tr>
<tr>
<td>Atypical Antipsychotic</td>
<td>Aripiprazole, Risperidone, Quetiapine, Olanzapine</td>
<td>Block dopamine pathways (less likely to cause extrapyramidal side effects)</td>
</tr>
<tr>
<td>Typical Antipsychotic</td>
<td>Haloperidol, Loxapine</td>
<td>Block dopamine pathways (likely to cause</td>
</tr>
<tr>
<td>Mood Stabilizer</td>
<td><strong>Valproic Acid</strong>, Lamotrigine</td>
<td>extrapyramidal side effects</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
</tr>
</tbody>
</table>

Block voltage-gated sodium channels, affecting the brain's glutamate system. Some may be more related to effects on the GABA system.

*Bold Font:* Medications prescribed to participants in the current study (n=185)
Table 4.3. Treated Prevalence of Depression According to Various Cut-points on Three Depression Questionnaires

<table>
<thead>
<tr>
<th>Questionnaire (Cut-point Score)</th>
<th>Treated Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 (10)</td>
<td>37.8</td>
</tr>
<tr>
<td>PHQ-9 (9)</td>
<td>37.8</td>
</tr>
<tr>
<td>PHQ-9 (11)</td>
<td>38.7</td>
</tr>
<tr>
<td>PHQ-9 (12)</td>
<td>44.0</td>
</tr>
<tr>
<td>PHQ-2 (3)</td>
<td>32.3</td>
</tr>
<tr>
<td>PHQ-9 Algorithm</td>
<td>18.2</td>
</tr>
<tr>
<td>HADS (8)</td>
<td>35.5</td>
</tr>
<tr>
<td>HADS (7)</td>
<td>32.6</td>
</tr>
<tr>
<td>HADS (6)</td>
<td>32.1</td>
</tr>
</tbody>
</table>

Note: PHQ: Patient Health Questionnaire; HADS: Hospital Anxiety and Depression Scale
### Table 4.4. List of Anti-Epileptic Medications

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Block Sodium Channels</th>
<th>Enhance GABA-Mediated Chloride Currents</th>
<th>Block T-Calcium Channels</th>
<th>Block Glutamate-Mediated Channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-/?.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-/?.</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-/?.</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>+/?</td>
<td>+/-</td>
<td>-</td>
<td>-/?.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>++</td>
<td>-/?</td>
<td>-/?</td>
<td>+/?.</td>
</tr>
<tr>
<td>Leviteracetam</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phenobarbitol</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-/?.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-/?.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>++</td>
<td>+/?</td>
<td>-</td>
<td>+/?.</td>
</tr>
<tr>
<td>Valproate</td>
<td>++</td>
<td>+/?</td>
<td>-/?</td>
<td>-/?.</td>
</tr>
</tbody>
</table>

Table adapted from Bromfield et al., 2006 [39]

++: Major action; +: Definite action, moderate; +/?: Possible action; -/?: Unknown, probably no action; -: no action

**Bold Font:** Medications prescribed to participants in the current study (n=185)
## Appendix 1. Current Medications (Psychotropic and Anti-Epileptic) in Persons with Current Depression (N=27)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Psychotropic</th>
<th>Anti-Epileptic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>---</td>
<td>Topiramate</td>
</tr>
<tr>
<td>2</td>
<td>---</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>3</td>
<td>Citalopram</td>
<td>Clobazam, Leviteracetam</td>
</tr>
<tr>
<td>4</td>
<td>Escitalopram, Trazodone</td>
<td>Phenytoin, Clonazepam</td>
</tr>
<tr>
<td>5</td>
<td>---</td>
<td>Carbemazepine</td>
</tr>
<tr>
<td>6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>Quetiapine, Sertraline, Mirtazapine</td>
<td>Clonazepam, Topiramate, Lacosamide</td>
</tr>
<tr>
<td>9</td>
<td>---</td>
<td>Clobazam, Lamotrigine, Topiramate</td>
</tr>
<tr>
<td>10</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>11</td>
<td>---</td>
<td>Lamotrigine, Topiramate</td>
</tr>
<tr>
<td>12</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>13</td>
<td>---</td>
<td>Divalproex Sodium, Carbemazepine</td>
</tr>
<tr>
<td>14</td>
<td>---</td>
<td>Leviteracetam</td>
</tr>
<tr>
<td>15</td>
<td>Lorazepam</td>
<td>Topiramate</td>
</tr>
<tr>
<td>16</td>
<td>---</td>
<td>Phenytoin, Topiramate</td>
</tr>
<tr>
<td>17</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>18</td>
<td>---</td>
<td>Clonazepam, Lamotrigine, Leviteracetam, Topiramate</td>
</tr>
<tr>
<td>19</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>20</td>
<td>---</td>
<td>Carbemazepine</td>
</tr>
<tr>
<td>21</td>
<td>---</td>
<td>Lamotrigine, Leviteracetam</td>
</tr>
<tr>
<td>22</td>
<td>---</td>
<td>Divalproex Sodium</td>
</tr>
<tr>
<td>23</td>
<td>---</td>
<td>Carbemazepine</td>
</tr>
<tr>
<td>24</td>
<td>Citalopram</td>
<td>Phenytoin, Clobazam</td>
</tr>
<tr>
<td>25</td>
<td>---</td>
<td>Topiramate</td>
</tr>
<tr>
<td>26</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>27</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
</tbody>
</table>
# Appendix 2. Current Medications (Psychotropic and Anti-Epileptic) in Persons with Past Depression (N=51)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Psychotropic</th>
<th>Anti-Epileptic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>---</td>
<td>Topiramate</td>
</tr>
<tr>
<td>2</td>
<td>---</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>3</td>
<td>---</td>
<td>Clonazepam, Lamotrigine, Leviteracetam, Topiramate</td>
</tr>
<tr>
<td>4</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>5</td>
<td>---</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>6</td>
<td>Citalopram</td>
<td>Clobazam, Leviteracetam</td>
</tr>
<tr>
<td>7</td>
<td>Quetiapine, Sertraline, Mirtazapine</td>
<td>Clonazepam, Lacosamide</td>
</tr>
<tr>
<td>8</td>
<td>---</td>
<td>Topiramate</td>
</tr>
<tr>
<td>9</td>
<td>---</td>
<td>Divalproex Sodium, Lamotrigine</td>
</tr>
<tr>
<td>10</td>
<td>---</td>
<td>Lamotrigine, Leviteracetam</td>
</tr>
<tr>
<td>11</td>
<td>---</td>
<td>Divalproex Sodium, Carbamazepine</td>
</tr>
<tr>
<td>12</td>
<td>Paroxetine</td>
<td>Lorazepam, Lamotrigine</td>
</tr>
<tr>
<td>13</td>
<td>---</td>
<td>Divalproex Sodium</td>
</tr>
<tr>
<td>14</td>
<td>Venlafaxine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>15</td>
<td>Aripiprazole, Quetiapine</td>
<td>Divalproex Sodium</td>
</tr>
<tr>
<td>16</td>
<td>---</td>
<td>Divalproex Sodium, Topiramate</td>
</tr>
<tr>
<td>17</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>18</td>
<td>---</td>
<td>Leviteracetam</td>
</tr>
<tr>
<td>19</td>
<td>---</td>
<td>Clobazam, Carbamazepine</td>
</tr>
<tr>
<td>20</td>
<td>---</td>
<td>Lamotrigine</td>
</tr>
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<td>21</td>
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CHAPTER 5: DISCUSSION
5.1 Summary of Main Findings

This dissertation addresses several important questions about the relationship between depression and epilepsy using multiple methodologies and data sources. Paper 1 estimated the prevalence of depression in epilepsy and the magnitude of the association, paper 2 examined the validity of three depression screening tools and cut-points for scoring these tools in a population of PWE and paper 3 investigated the treated prevalence of depression in epilepsy and methods of treatment used.

The objective of paper 1 was to estimate the prevalence and burden of depression in PWE based on previously published population-based studies. A systematic review of the literature was conducted and all abstracts and full-text articles were reviewed in duplicate. Over 7000 abstracts were reviewed, and data from 14 unique sources were abstracted. The overall prevalence of active depression in PWE was 23.1%, with a pooled odds ratio (OR) of 2.77. All studies reported a prevalence of depression greater than that found in the general population and all lower limits of the estimated confidence intervals were greater than one. In addition, the lower bound of the 95% confidence interval for the pooled OR was 2.09, indicating a significant relationship with even the most conservative interpretation. This population-based study highlights the burden of depression in all PWE, not only those from a select clinical population.

Paper 2 aimed to validate depression-screening tools in PWE using a gold-standard diagnostic instrument, the SCID, and to explore new cut-points for scoring. Patients for this study were recruited from the only epilepsy clinic in a large, urban health region serving a population of over one million persons. All participants completed a questionnaire package in clinic that included information on demographics, two depression screening tools (PHQ-9 and HADS) and a quality of life questionnaire (SF-12). Those who consented also completed a gold-
standard psychiatric interview over the phone within two weeks of their clinic appointment (N=185). Selecting the appropriate tool for use in clinic populations depends on the intended outcome; the scale with the highest specificity was the PHQ-9 algorithm method and the highest sensitivity was observed in the HADS with a cut-point of six. Cut-points indicative of depression in the general population (10/27 on the PHQ-9; 8 out of 21 on the HADS) resulted in suboptimal sensitivities in PWE. The appropriate cut-point should be chosen based on the goals of the application and available resources. For example, if false negatives are a concern and resources are plentiful, then it would be important to maximize sensitivity and the HADS with a cut-point of six could be employed. In an environment where mental health resources are scarce and there may be concerns about incorrect diagnosis and treatment, false positives should be minimized and specificity optimized; in this case the PHQ-9 with the algorithm scoring method is the best method. The greatest balance of sensitivity and specificity was achieved on the PHQ-9 with a cut-point of nine and the HADS with a cut-point of seven. The optimal tool will depend on many factors, including the goals of the study and the resources available.

Interestingly, the prevalence of depression in epilepsy found in paper 2 (14.6%) was much lower than the pooled estimate from paper 1 (23.1%). Since the sample for paper 2 is from a clinic, their symptoms and disease state are likely to be worse than those in the general population from paper 1. One would expect, then, for the prevalence of depression in epilepsy to be higher in paper 2. This may be explained by the rigour of the depression diagnosis from paper 2; the SCID is a semi-structured interview with very strict criteria, whereas most studies found in paper 1 rely on self-report of depression. The prevalence of depression on the different self-report scales from paper 2 (HADS: 17.2%, PHQ-9 cut-point: 21.9%, self-report: 25.4%) is much
closer to the pooled estimate from paper 1. It is evident that a great amount of the observed heterogeneity between studies is due to the method of diagnosing depression.

Though research has shown that the prevalence of depression in epilepsy is high, and that methods exist to easily identify depression in this population, the majority of PWE with depression are untreated. Paper 3 estimated the prevalence of treated depression in PWE and characterized the methods by which depression was managed in this population. The population used in paper 2 was also analyzed for this third objective - 185 consecutive eligible PWE from an outpatient epilepsy clinic. Treatment for depression was assessed using both patient self-report and medical chart review of both pharmacological and non-pharmacological treatment. The majority of PWE with current depression (70.3%) were not being treated. Of those who were treated, most were receiving non-pharmacological over pharmacological treatment. More individuals with a past history of depression (as opposed to current) were treated (37.2%) and it was more common for these patients to be treated with medication. If a PWE has comorbid depression, pharmacological and/or non-pharmacological treatment should be explored as treatment options.

The papers presented in this dissertation represent an investigation into the magnitude of depression in epilepsy, methods for identifying those individuals who are depressed and a characterization of the prevalence and methods of treatment employed.

5.2 Challenges and Limitations in Studying the Association between Depression and Epilepsy

There has been a great amount of research into the association between depression and epilepsy in recent years, from both the basic and clinical neurosciences. A number of hypotheses have been posited explaining this relationship, and it is evident that common pathogenic
mechanisms exist. These may include: (1) a hyperactive HPA axis; (2) disturbances in neurotransmitter systems; (3) structural changes to cerebral structures; and (4) functional abnormalities in common cerebral areas[37, 45]. These complex mechanisms make disentangling the relationship quite difficult, and it is likely no one mechanism operates alone.

Research has consistently reported a high prevalence and large magnitude of association between depression and epilepsy, regardless of the population studied and methods of disease diagnosis. Based on the number of studies reporting on the population-based prevalence of depression in epilepsy found through the systematic review in Paper 1, there is no longer a need to quantify the relationship in this manner.

Interestingly, although the prevalence of depression in epilepsy is high, the contribution of depression alone to the global burden of disease has decreased. In 1990, depression was the fourth-leading contributor to disability-adjusted life-years worldwide[82]; in an updated 2010 study, it ranked 11th[17]. It is likely that the change in the relative contribution of depression to the global burden of disease is related to the increase in the contribution of other conditions, such as heart disease and stroke.

The most striking finding from the systematic review was the heterogeneity present between different prevalence estimates of depression, according to the method of assessment of both depression ($I^2 = 97.7\%, p < .0001$) and epilepsy ($I^2 = 97.7\%, p < .0001$). As with the findings from Paper 2, there is no “best” tool to assess the prevalence of depression in epidemiologic studies. The method of assessment will depend on the available data (administrative database, community survey) and resources. Clinical interviews for depression, which are considered the gold standard in research, are unlikely to be feasible in large epidemiologic studies. Since the goal of these studies is to identify as many people with
depression as possible, the method chosen should have a high sensitivity and reduce false negative results. Common operational definitions of both epilepsy and depression would aid in the comparison of epidemiologic studies, and researchers in this area should refer to the ILAE Epidemiology Commission standards for reporting on epidemiologic studies of epilepsy[7].

One of the most common criticisms of general depression screening tools for detecting depression in epilepsy is the overlap of depressive symptoms and the side effects of some AEDs[37]. It is hypothesized that because some symptoms of depression, such as fatigue, sleeping difficulties and issues with concentration, are also side effects of AEDs, PWE may screen positive on depression tools when they are not actually depressed[37]. Disease-specific depression tools, such as the NDDI-E[59], are suggested as an alternative to the general tools used in the current study because it does not include somatic or cognitive symptoms of depression. This study found significantly greater proportion of persons with depression reporting side effects of AEDs, relative to those without depression; interestingly, not everyone who reported depression as a side effect of their medication was currently depressed. It is possible, though, that by modifying the cut-points used to determine a diagnosis of depression based on a screening tool, that these problems may be mitigated.

The adequacy and appropriateness of depression treatment was not assessed in the current study. The definition of treated depression in this population was purposefully over-inclusive; the definition included those persons on any medication with psychotropic properties, regardless of the indication or dosage. The justification for this definition was to ensure that the psychotropic effects of all drugs be taken into account, regardless of the desired purpose. It is possible that the medication was not being used for depression, nor at a dose that would be expected to treat depression; for example, if an individual was on 20 mg amitriptyline at bedtime
for headache prophylaxis, that dose would not be expected to treat depression. The overlap in indications of many anti-epileptic and psychotropic medications further complicates this issue, as commonly prescribed AEDs (lamotrigine, clonazepam, levetiracetam) have known psychotropic effects. In Paper 3 the actual proportion receiving treatment for depression may be even lower than estimated, if the appropriateness and adequacy of the medication were also taken into account.

Future studies should identify people with epilepsy who are not being treated for depression, and in those who are treated, investigate how depression is currently being managed. The type of medication and dosage should be measured to determine if treatment is at a therapeutic dose, and that the correct medications are being used to treat depression in epilepsy. It is also necessary to note non-pharmacologic treatments for depression, as they have been shown effective in reducing depressive symptoms in PWE [68, 73]. This information is essential for future research, as a benchmark for assessing the uptake of treatment and to identify barriers to treatment in this population. It is necessary to understand the current status of all types of depression management in epilepsy (pharmacological and non-pharmacological) to measure changes in use over time. Patterns in both the amount and type of treatment used are important for resource planning and identifying reasons for the lack of treatment in certain populations.

Epilepsy surgery may further complicate the study of depression and epilepsy, as there are numerous established psychiatric effects pre- and post-surgery. Individuals with pre-operative major depression are more likely to have a non-favourable seizure outcome post temporal lobe resection (OR=5.23) [83]. After resective surgery, participants show an initial improvement in depressive symptoms, though at 60 months follow-up only those with good or excellent seizure control show a long-term improvement in mood [84]. The mechanisms
underlying this effect are still unclear, though surgical research further supports the bi-directional relationship between depression and epilepsy.

5.3 Clinical and Public Health Implications

One goal of health research is to positively impact clinical and public health outcomes through intervention. These interventions are typically targeted at disease prevention, and can be divided into three levels: primary, secondary and tertiary[74]. Primary prevention focuses on reducing disease incidence, typically through population-level education strategies. Secondary prevention aims to intervene early in the disease process, through early detection and treatment. Tertiary prevention plans interventions after the disease process is initiated, to minimize the burden and negative impact of disease. The results of this dissertation focus mainly on secondary prevention, identifying the depression early in its course and treating these persons in a timely manner.

By estimating the pooled prevalence and the magnitude of the association, Paper 1 has quantified the burden of depression in epilepsy. An understanding of this association can help with resource planning and allocation. Knowledge of the population-based prevalence of depression in epilepsy may be useful for policy makers. By understanding the burden of disease, resources may be allocated more effectively. For example, if 25% of persons with epilepsy also have active depression, it may be a more effective use of resources to accurately identify and treat them early in the disease process. Persons with epilepsy with unrecognized or untreated depression use more health resources than those without depression[30]. If symptoms are identified and adequately treated initially, health care system visits for both medical and psychiatric reasons may be reduced; this may ultimately make the system more efficient and save on medical costs.
Another outcome of the systematic review and meta-analysis of the population-based prevalence of depression in epilepsy is the utility of the pooled prevalence in estimating the performance of depression scales in persons with epilepsy. Bayes theorem is often used in epidemiology to obtain the probability of a disease in a group of people with a specific characteristic based on the overall proportion of that disease in the population, and the likelihood of that characteristic being present in those with and without the disease[74]. In this case, estimating the prevalence of depression based on depression screening tools relative to that of a gold standard diagnosis of depression. The pooled prevalence of 25%, then, is our best estimate of the base-rate of depression in epilepsy. An important component of this formula is that the probability of disease, given a certain characteristic, is dependent not only on how common that characteristic is in the disease, but also the frequency of disease in the total population. One note of caution is that this pooled prevalence of depression is population-based, and estimates of depression in epilepsy may be higher in clinic-based samples where the severity of disease may be worse.

Paper 2 presents an assessment of the suitability of a variety of tools to identify depression in PWE. These self-report tools are often used in screening, a form of secondary prevention, to identify individuals who have a disorder that is not yet clinically apparent[55, 56]. As previously mentioned, for screening to be effective, it must fulfill a number of criteria: (a) it should produce a better prognosis than if it were detected and treated later; (b) it should be relatively inexpensive and quick; (c) it should not result in many false positives, which could lead to inappropriate treatment, increased burden to the health care system and the potential of being stigmatized and labeled; (d) it should be important and prevalent, and cannot be easily
detected without screening; and (e) there should be appropriate, available and effective follow-up treatment[47, 69].

Recommended screening instruments for depression in epilepsy are publically available at no cost (PHQ-9), and typically take less than five minutes to complete[72]. The high prevalence of depression in epilepsy (25% in the general population) will lead to an elevated positive predictive value (PPV) (the probability that those who test positive have the disease in question). Bayes theorem demonstrates that the greater the prevalence of disease in a population, the higher the PPV[74].

\[
PPV \% = \frac{(Prevalence \times Sensitivity)}{(Prevalence \times Sensitivity) + [(1 - Prevalence) \times (1 - Specificity)]}
\]

Using a base-rate (prevalence) of depression in epilepsy of 25% and the sensitivity (80.8%) and specificity (85.1%) from the HADS with a cut-point of seven, the PPV of the tool can be calculated. Sixty-five percent of people with a positive result on the depression screening test will also have depression according to the gold standard in this scenario. Whether this represents a reasonable PPV depends on the resources available, as false positives can be expected in 45% of those with a positive result. It should be noted, however, that many of the false positives may have significant psychosocial issues and it may not be a waste of resources for them to be assessed.

Depression is also difficult to diagnose quickly in a clinical setting without the use of a screening tool. Many treatments for depression in epilepsy exist, including most selective serotonin re-uptake inhibitors (SSRIs) and non-pharmacological management (eg. Cognitive behavioural therapy) with an expert, such as a neuropsychiatrist or psychologist[65]. Taking this into account, screening for depression in persons with epilepsy should be considered in clinical
settings where persons with epilepsy are regularly followed. The first step in this consideration involves establishing the feasibility of such a program in the ascribed clinical setting.

The implementation of screening in clinics will vary, and depend on resource availability; a rigid, formal screening process would likely be cumbersome, time consuming and costly. To ensure depressed persons with epilepsy are adequately identified and treated, a stepped-care approach (treatment that is augmented depending on disease severity) is recommended [78]. The feasibility of having patients fill out a brief questionnaire has been demonstrated in the studies in this dissertation, which are also quick to score and interpret. All patients should be screened for depression, including those persons who have exhibited symptoms in the past. If a person with epilepsy screens positive for depression on a screening tool, a number of factors must be considered before treatment of any kind is initiated. If depressive symptoms are persistent and interfere with a patient’s daily social, occupational or family functioning (part of the DSM criteria for a major depressive episode) (APA, 2013), AEDs should be reviewed to determine if they are a contributing factor to the depression. Medications such as levetiracetam are known to have negative psychotropic effects in persons with epilepsy[65]. Physicians can determine if optimizing AEDs may alleviate the depressive symptoms. If these interventions are not effective, then the severity of a person’s depression may dictate the next steps in care; in persons with epilepsy who are severely depressed or experiencing suicidal thoughts, a referral to a psychiatrist or psychologist, or even hospital admission, may be immediately appropriate. In the case of less severe episodes of depression, the attending physician may decide to treat the condition themselves; the most commonly prescribed class of anti-depressants for persons with epilepsy are SSRIs. It is recommended that these medications be initiated at the lowest possible therapeutic dose. Persons with epilepsy may also be referred to cost-effective non-
pharmacological treatments, such as group cognitive behavioural therapy. Certain situations may require the consultation of a psychiatrist or psychologist; ideally, however, this stepped care approach would reduce unnecessary contacts with limited-resource positions. Stepped care for depression treatment has been positively evaluated in some settings, including primary care[78], the elderly [79] and persons with diabetes[80]; it should also be assessed for use in epilepsy populations.

The impact of screening should also be considered, as there are implications for patient outcomes and health-resource utilization. Research suggests that outcomes may be improved if depression is properly treated in persons with epilepsy; quality of life may improve and seizures may be more well controlled[75]. By screening for depression, depressed individuals may be identified earlier in the disease process, and treatment may be initiated sooner than with usual care. Screening, as with any health intervention, involves the use of resources, though ultimately it would hope to reduce the burden on the healthcare system. These steps are recommended for use in outpatient neurological settings where persons with epilepsy are the main population seen. In general practice, these measures are unlikely to be effective. The number of persons with epilepsy in these settings would be lower, relative to an outpatient clinic. In addition, the epilepsy is likely to be less severe if they do not require follow-up with a specialist. These are important considerations when implementing a screening program.

By investigating the treatment of depression in epilepsy, paper 3 focuses on tertiary prevention; intervening to reduce the negative outcomes of disease and improve quality of life. Depression has a greater impact on quality of life in PWE than seizure frequency[43]; depression is very common, severe, underdiagnosed and untreated in PWE[43]. Cognitive behavioral therapy, the most commonly studied non-pharmacological treatment for epilepsy, can improve
quality of life, and other health behaviours (such as adherence to medication) that may trigger seizures[75]. Research has shown that PWE who have untreated comorbid depression use more health services than those who are not depressed[30]. These individuals have more visits to the doctor for both medical and psychiatric indications[30]. The greatest use of health services is by persons with the most severe symptoms of depression[30]. To determine the effectiveness of treatment for improving these outcomes, persons with epilepsy should be followed over time, and their health resource use recorded.

**5.4 Directions for Future Research**

The majority of current epidemiological research remains focused on accurately identifying depression in persons with epilepsy. Investigating the most efficient and exact method of diagnosing depression in epilepsy is very important, but until all available depression screening tools are directly compared to each other in the same population, definitive conclusions cannot be made.

A direct comparison of disease-specific and general depression screening tools is therefore essential. A study similar to that conducted for Papers 2 and 3 should be carried out to compare these tools. Participants should be consecutively recruited from an outpatient epilepsy clinic and consent to a medical chart review, questionnaire package and clinical interview. The medical chart review will allow for the comparison of epilepsy-specific characteristics, such as seizure frequency and anti-epileptic medication, and pharmacological and non-pharmacological management of depression. The questionnaire package would include important outcome measures such as quality of life and self-reported disease severity, along with disease-specific and general depression screening tools. Ideally, all participants would complete the NDDI-E, PHQ-9, HADS and other tools used in epilepsy research, such as the BDI and CES-D in a
randomized order, to address order effects of filling out multiple depression questionnaires. Following the questionnaire, the SCID would be given to all consenting participants (over the phone to enhance feasibility) at their earliest convenience. All scales would be directly compared to the SCID to determine their performance in this population, using sensitivity, specificity, positive predictive value, negative predictive value and area under the curve analyses. As with Paper 2, the appropriate scale to screen for depression in epilepsy will depend on the goals, setting and resources available to future projects.

To determine the effectiveness of depression screening, a follow-up study in persons with epilepsy is required. The sample for this study must be as similar as possible to that in which the screening tools were validated. In a setting where a stepped-care plan is employed, and resources are available, a tool that minimizes false negatives is most appropriate. The results of paper 2 indicate that the HADS with a cut-point of six had the highest sensitivity (84.6%) in an outpatient population with epilepsy. If resources are limited, a scale with high specificity (to minimize false positives), such as the PHQ-9 with the algorithm scoring method, is more appropriate. The goal of screening is to identify those persons who are currently depressed, but have not been previously identified or treated; these individuals would form the sample of the study. Currently depressed persons would be followed over time to see if identification and treatment improves their depressive symptoms. Other important health outcomes, such as quality of life and seizure frequency would also be assessed over time. For screening to be considered effective, these persons would see a marked decrease in depressive symptoms and an increase in important health outcomes. As with all studies, there would be limitations to this work, including the likelihood of false positives due to less than perfect specificity in screening tools. False positives may divert resources and lead to improper treatment of depression; it is recommended
that depressive symptoms be monitored over time to reduce the likelihood of this possibility. To further establish the effectiveness of screening, a randomized controlled trial (RCT) of the screening protocol, along with an economic evaluation, would also be warranted.

There is a relative dearth of information into the treatment of depression in persons with epilepsy. The only RCT of anti-depressants in persons with epilepsy was conducted almost 30 years ago using rarely prescribed medications for depression, one of which has since been removed from the market[76, 77]. An RCT of newer anti-depressants for treating depression in persons with epilepsy (SSRIs) is urgently needed, as current recommendations for treatment are not based on randomized trial data. In addition, pharmacological therapy for treating depression needs to be directly compared to non-pharmacological management in a population of persons with epilepsy. Pharmacological and non-pharmacological management, and a combination of both for treating depression should be evaluated in multiple RCTs to definitively establish treatment recommendations.

The first study comparing pharmacological and non-pharmacological treatments for depression in epilepsy would be conceptualized through consultation with experts in the field, policy makers and persons with epilepsy, and managed by a scientific advisory board. This trial should evaluate four randomly allocated interventions: (1) usual care; (2) non-pharmacological management (such as CBT); (3) pharmacological management (an SSRI, citalopram is recommended by current guidelines)[72]; and (4) a combination of non-pharmacological and pharmacological management. A diagnosis of depression and depressive symptoms would be the main outcomes of interest, though other important factors, such as quality of life, seizure frequency and perceived disease severity would also be measured. The individuals randomized to these groups would be followed over time to determine the effectiveness of each intervention
in eliminating depression or reducing depressive symptoms. This study would stimulate further trials of pharmacological and non-pharmacological interventions for treating depression in epilepsy. As with all RCTs, the applicability of the results to other populations would be limited; therefore, multiple studies, in a variety of populations and settings, would be required. The body of evidence from these trials would inform evidence-based guidelines on the treatment of depression in epilepsy.

Along with establishing treatment effectiveness, evaluating the influence of depression management on the health care system is also important. The health resource use of depressed persons with epilepsy should be followed before and after the introduction of treatments for depression. It is expected that adequately treated persons would see a reduction in their health services use for both psychiatric and medical reasons. A comparison of this use would help establish the long-term, system-wide benefits of proper depression management.

It is unclear how depression affects persons with epilepsy relative to other neurological conditions. In order to elucidate common pathophysiology, mechanisms and outcomes, the prevalence of depression should be evaluated in a number of neurological conditions using similar methodologies. Screening tools should be compared and outcomes assessed across conditions to establish if common assessment and intervention efforts may be employed.

The work conducted over the course of this dissertation has addressed several gaps in knowledge, including estimating the pooled prevalence of depression in persons with epilepsy and the magnitude of that association, assessing the diagnostic properties of multiple depression screening tools for use in persons with epilepsy, and describing the patterns of depression treatment in persons with epilepsy. Despite the existing state of knowledge, the current identification and management of depression in epilepsy continues to be less than ideal; by
building upon the results of this work, progress can be made for the care of persons with epilepsy.
REFERENCES


Appendix A: Student Contributions

As the first author of the three manuscripts presented in this dissertation, the student, Kirsten M. Fiest, contributed significantly to these works.

For Paper 1 (Chapter 2) I participated in the acquisition of data through the review of over 7000 abstracts and 150 full-text articles. I abstracted all data from the selected full-text articles and completed all of the data analysis for this project. Along with co-authors I interpreted the results of this study. I wrote the first draft of the manuscript and participated in the critical review of the paper.

For Papers 2 and 3 (Chapters 3 and 4) I conceived of the study design and recruitment process along with my supervisors. I participated in the recruitment of 300 persons with epilepsy from the Foothills Medical Center at the University of Calgary. Following their initial recruitment, I conducted over 150 psychiatric interviews over the phone with consenting patients. I cleaned all of the resulting data and prepared it for analysis. I completed all of the data analysis for both papers and interpreted the data. Finally, I wrote both manuscripts and incorporated co-author feedback for their improvement.
Appendix B: Epilepsy Clinic Preliminary Consent Form

A Research Assistant is on site today for a project funded by Alberta Health Services and the University of Calgary.

We are asking all Calgary patients seen in the clinic if they would be willing to help us by filling out a 5 - 10 minute questionnaire before their appointment, and learn more about a project aimed at improving care for those patients seen in our clinics.

Would you be willing to speak with our Research Assistant?

Thank you in advance for your consideration.

☐ Yes, I am willing to be approached by the study research assistant on site today.

__________________________________________  ________________________________
Participant’s Name  Signature and Date
Appendix C: Epilepsy Clinic Full Consent Form

Consent Form: The NEEDS Survey

TITLE: “NEEDS” Stands for NEurological disease and Depression Study (NEEDS) – Understanding and Addressing the burden, course and impact of depressive disorders in neurological conditions

SPONSOR: Faculty of Medicine, University of Calgary. Alberta Health Services

INVESTIGATORS: Dr. Nathalie Jetté and Dr. Scott Patten

CONTACT PHONE NUMBER: (403) 220-8752 or (403) 944-2760

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form.

BACKGROUND
Depression is a problem for a sizable proportion of people living with neurological conditions. The goal of this study is to identify better ways of helping people to overcome this problem. Our goal is to collect new information so that we can learn how to better address this problem. In order to provide accurate results, it is important to have a representative sample of people attending this clinic, irrespective what specific diagnosis they have or whether they are depressed or not.

**WHAT IS THE PURPOSE OF THE STUDY?**

Improving the way that services are delivered will require having a better understanding of the underlying problems. This study will determine how many people with various neurological conditions in the Calgary Health Zone have depressive symptoms, what questionnaires are best for identifying depression and what impact depression has on people’s functioning and quality of life.

**WHAT WOULD I HAVE TO DO?**

This study involves collecting data from two sources: (1) completing a questionnaire and (2) allowing us to review your chart to record diagnostic information. We also expect that this work will continue with later additional studies. Because the questionnaire is quite brief, we are interested in doing additional interviews in order to double-check the accuracy of some parts of it. At the bottom of the form there are checkboxes, indicating your willingness (or not) to participate in this part of the study, and another checkbox indicating your willingness to be
contacted in the future regarding future studies. More detail about these options is provided in the following paragraphs.

We are asking for your permission to review your file at the clinic in order to record the diagnosis that has been assigned by your neurologist. We feel that this will be the most accurate way to record diagnoses.

Second, participation in the study also involves completing a brief set of questionnaires (in total, these take approximately 10-15 minutes). This questionnaire includes the following elements:

Two ratings scales designed to detect symptoms of depression and to measure the severity of these symptoms.
A brief set of questions recording basic information: age, gender, education etc.
A questionnaire one to measure quality of life and difficulties that you may or may not be having with day to day functioning.

Third, a subset of survey participants will be asked to complete a second interview. This part is intended to assess how well the scales are working by comparing scores on the scales to the results of a more detailed assessment. This interview can be completed over the phone later at a time that is convenient to you. This interview would last 10-15 minutes and will ask detailed questions relevant to symptoms of depression.

WHAT ARE THE RISKS?
There are no risks associated with participation in the study. The survey does not involve treatment or any other type of intervention.

**WILL I BENEFIT IF I TAKE PART?**

If you agree to participate in this study there may or may not be a direct benefit to you. The information we get from this study may help us to provide better treatments in the future for people with neurological conditions that also have depression.

**DO I HAVE TO PARTICIPATE?**

Participation in this study is voluntary. Even if you sign this form you are free to withdraw at any time without jeopardizing their health care. This consent form, a copy of which will be provided to you, has contact information. Please let us know if you do not wish to participate further or if you do not wish to be contacted about further studies.

**WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?**

There are no costs associated with participation in this study.

**IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?**
In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Calgary, Alberta Health Services or the Researchers. You still have all your legal rights. Nothing said in this form alters your right to seek damages.

**WILL MY RECORDS BE KEPT PRIVATE?**

Only members of the investigative team will have access to information collected. When the study is completed (within the next year), the data collected will be compiled into a secure database (password protected) which will be stored in a secure location. Names and personally identifying information will be removed from the database and stored separately in a secure location. All data will be kept for a period of 12 years as per health records policy.

*Please check all that apply*

I provide permission for diagnostic information to be recorded from my file for purposes of this study.

I am willing to complete the study questionnaire.

I am willing to be contacted later if I am selected for an additional interview.
I provide permission to be contacted for possible later participation in additional studies.

I provide permission for the investigators to link my data to Alberta Health and Wellness or Alberta Health Services registries that include information about medical visits (e.g. hospital, emergency room, physician visits). These registries record reason or diagnosis for each medical visit. All these data will be provided to us de-identified, meaning they will be completely anonymous.

Preferred method of contact: ________________________________________

Preferred day/time of contact: ________________________________

Email address: ________________________________________

Phone number: ______________________________________

Mailing address: ________________________________________
SIGNATURES

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. If you have further questions concerning matters related to this research, please contact:

Dr. Nathalie Jetté (403) 944-2760 or Dr. Scott Patten (403) 220-8752

If you have any questions concerning your rights as a possible participant in this research, please contact The Chair of the Conjoint Health Research Ethics Board at the Office of Medical Bioethics, 403-220-7990 or the Ethics Resource Officer, Internal Awards, Research Services, University of Calgary, at 403-220-3782.
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Investigator/Delegate’s Name</td>
<td>Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name</td>
<td>Signature and Date</td>
</tr>
</tbody>
</table>
Appendix D: Questionnaire Package

DEMOGRAPHICS

Thank you for taking the time to complete this questionnaire. Due to the nature of the study, some of the questions below will seem very similar. Please answer each question based on its own merits.

1. Which of the following best describes your current marital status? (check one)

☐ Married ☐ Separated ☐ Divorced ☐ Widowed
☐ Common-law (living together) ☐ Single, never married

2. What is the highest grade, degree, certificate or diploma that you have ever completed?

☐ Grade 8 or lower ☐ Trade certificate or diploma from a vocational school or apprenticeship training
☐ Grade 9-11 ☐ Non-university certificate or diploma from a community college, CEGEP, school or nursing
☐ Grade 12-13 ☐ University certificate below bachelor’s level
☐ Bachelor’s degree ☐ University degree or certificate above bachelor’s level

3. Are you currently working in a paid job? Please include part-time jobs, seasonal work, contract work, self-employment, baby-sitting and any other paid work, regardless of number of hours worked.

☐ Yes ☐ No

4. What is your primary source of income? (check one)

☐ Employment ☐ Social Services ☐ Spouse/Family Support
☐ AISH ☐ Retirement Pension ☐ Disability Insurance ☐ Investment/Savings

5. Do you ever drink alcohol (e.g. beer, wine or spirits)? (check one)

☐ Yes ☐ No
6. Do you currently smoke cigarettes? (check one)

☐ Yes  ☐ No

7. Do you use illicit drugs such as marijuana or cocaine? (check one)

☐ Yes  ☐ No

**CLINICAL BACKGROUND**

8. Do you have side-effects to any of your current medications?

☐ Yes  ☐ No

9. Have you been diagnosed with depression by a health professional? (check one)

☐ Yes- please answer questions 10-12  ☐ No- go to next page

10. Who is currently managing (treating) your depression? (select all that apply)

☐ My family physician is managing my depression

☐ A psychiatrist is managing my depression

☐ Another specialist is managing my depression. Please specify specialty (e.g. Neurologist):

_________________________________________

☐ A counselor is managing my depression. Please specify the type of counselor (e.g. Social Worker):

_________________________________________

☐ Another person is managing my depression. Please specify that person’s profession (e.g. a Nurse)

_________________________________________

☐ A psychologist is managing my depression

☐ I do not currently have anyone managing my depression

11. Are you currently taking any anti-depressant medications (e.g. Celexa, Effexor, etc.)?
12. Are you currently receiving other forms of treatment for your depression? Please select all that apply.

- Medications
- Counseling
- Talk Therapy (cognitive behavioral therapy)
- Group Therapy
- Other - please specify: ____________________________________________
DISEASE SEVERITY SCALE

Taking into account all aspects of your condition (e.g. epilepsy, or other condition for which you are seeing a neurologist), how would you rate its severity now? (check one)

- [ ] Extremely severe
- [ ] Very severe
- [ ] Quite severe
- [ ] Moderately severe
- [ ] Somewhat severe
- [ ] A little severe
- [ ] Not at all severe

Have you been diagnosed with a seizure disorder/epilepsy?

- [ ] No  [ ] Yes

If yes, taking into account all aspects of your seizures, how disabling are they? (check one)

- [ ] Extremely disabling
- [ ] Very disabling
- [ ] Quite disabling
- [ ] Moderately disabling
- [ ] Somewhat disabling
- [ ] A little disabling
- [ ] Not at all disabling
PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Check the response that most closely applies to you)

<table>
<thead>
<tr>
<th></th>
<th>Not At All</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Feeling bad about yourself— or that you are a failure or have let yourself or your family down</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or, being so fidgety or restless that you have been moving around a lot more than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. If you checked off any problems (questions 1-9), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- [ ] Not difficult at all
- [ ] Somewhat difficult
- [ ] Very difficult
- [ ] Extremely difficult
ADVERSE EVENT PROFILE (EPILEPSY)

During the past four weeks, have you had any of the problems or side-effects listed below?

For each item, if it has always or often been a problem, choose 4; if it has sometimes been a problem, choose 3; if it is rarely a problem, choose 2; if it is never a problem, choose 1. Please be sure to answer every item.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Always or Often a Problem</th>
<th>Sometimes a Problem</th>
<th>Rarely a Problem</th>
<th>Never a Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsteadiness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tiredness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Feelings of aggression</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervousness and/or agitation</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hair loss</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Problems with skin, e.g. acne, rash</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Double or blurred vision</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Upset stomach</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty in concentrating</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Trouble with mouth or gums</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Shaky hands</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Disturbed Sleep</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
**NEEDS Data Abstraction Form for Epilepsy Clinic**

**Reviewer:**

**Date:**  
YYYY, MM, DD

**Main Neurological Diagnosis**

**Date of Disease Onset**  (Please enter date of first seizure)

YYYY

**Epilepsy Syndrome (if applicable)**

- [ ] Epilepsy due to a genetic cause  
  Specify: ______________________  

- [ ] Epilepsy due to a structural-metabolic cause  
  Specify: ______________________  

- [ ] Epilepsy due to an unknown cause  
  Specify: ______________________  

- [ ] Not applicable (patient does not have epilepsy)

**Seizure Type (check all that apply)**

- [ ] Generalized Seizures  
  - [ ] Tonic-Clonic  
  - [ ] Absence
□ Clonic
□ Tonic
□ Atonic
□ Myoclonic
  □ Myoclonic
  □ Myoclonic-atonic
  □ Myoclonic-tonic
□ Focal Seizures
□ Epileptic Spasms
□ Unknown
□ Other Please Specify: __________________________________________
□ Not applicable (patient does not have epilepsy)

### Seizure Frequency (average, if applicable)

_______ of events per _________ ___

#  day, month or year

### Psychotropic Medications

#### Antipsychotics

**Typical Antipsychotics**

□ Haldol/haloperidol
□ Loxitane; Loxapac/loxapine
□ Moban/molindone
□ Prolixin/fluphenazine

**Atypical Antipsychotics**

□ Abilify/ aripiprazole
□ Geodon; Zeldox/ziprasidone
□ Invega/ paliperidone
□ Risperdal/ risperidone
□ Seroquel/ quetiapine
<table>
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<tr>
<th><strong>Stelazine/trifluoperazone</strong></th>
<th><strong>Zyprexa/olanzapine</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Thorazine/chlorpromazine</strong></td>
<td><strong>Zyprexa/olanzapine</strong></td>
</tr>
<tr>
<td><strong>Trilafon/perphenazine</strong></td>
<td><strong>Zyprexa/olanzapine</strong></td>
</tr>
</tbody>
</table>

**Other**
- **Clozaril/clozapine**

### Antidepressants

#### Tricyclic Antidepressants
- **Anafranil/clomipramine**
- **Elavil/amitriptyline**
- **Norpramin/desipramine**
- **Pamelor/nortriptyline**
- **Sinequan/doxepine**
- **Tofranil/imipramine**

#### SSRIs
- **Celexa/citalopram**
- **Lexapro; Cipralex/escitalopram**
- **Luvox/fluvoxamine**
- **Paxil/paroxetine**
- **Prozac/fluoxetine**
- **Zoloft/sertraline**

#### SNRIs
- **Cymbalta/duloxetine**
- **Effexor/venlafaxine**
- **Pristiq/desvenlafaxine**

#### Bupropion
- **Wellbutrin; Zyban/bupropion**

#### Other
- **Desyrel/Trazodone**
- **Remeron/Mirtazapine**

### Benzodiazepines & Related Sedative-Hypnotics

- **Ativan/lorazepam**
- **Imovane; Lunesta/zopiclone**
- **Klonopin; Rivotrol/clonazepam**
- **Librium/chlordiazepoxide**
- **Restoril/temazepam**
- **Sonata; Starnoc/zaleplon**
- **Serax/oxazepam**
- **Tranxene/clorazepate**
- **Valium/diazepam**
- **Xanax/alprazolam**
### Mood Stabilizers

- □ Epival; Depakote/Valproic Acid/Divalproex Sodium
- □ Lamictal/ lamotrigine
- □ Lithium
- □ Tegretol/carbamazepine

### Current Disease Specific Medications

#### Anti-epileptic Drugs

- □ Ativan/lorazepam
- □ Banzel/ rufinamide
- □ Dilantin/ phenytoin
- □ Epival; Depakote/ Valproic Acid
- □ Felbatol/ felbamate
- □ Frisium/ clobazam
- □ Klonopin; Rivotril/clonazepam
- □ Lamictal/ lamotrigine
- □ Lyrica/ pregablin
- □ Keppra/ levetiracetem
- □ Mysoline/ primidone
- □ Neurontin/ gabapentin
- □ Phenobarbital
- □ Sabril/ vigabatrin
- □ Tegretol/ carbamazepine
- □ Topamax/ topiramate
- □ Trileptal/ oxcarbazepine
- □ Vimpat/ lacosamide
- □ Zarontin/ ethosuximide
- □ Other:___________________
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Subject: RE: Permission to Use Paper in Thesis
Date: Wednesday, 5 March, 2014 6:52:37 PM Mountain Standard Time
From: Andrew G.M. Bulloch
To: Gilad G. Kaplan, Kirsten Fiest, Scott B. Patten, Samuel Wiebe, Colleen Maxwell, Nathalie Jette,

...mine too Kirsten...

Andrew G.M. Bulloch, PhD
Professor

From: Gilad G. Kaplan
Sent: March-05-14 1:57 PM
To: Kirsten Fiest; Scott B. Patten; Samuel Wiebe; Colleen Maxwell; Andrew G.M. Bulloch; Nathalie Jette;

Subject: RE: Permission to Use Paper in Thesis

You have my permission.
Gil

From: Kirsten Fiest
Sent: Wednesday, March 05, 2014 1:22 PM
To: Scott B. Patten; Samuel Wiebe; Colleen Maxwell; Andrew G.M. Bulloch; Nathalie Jette; Gilad G. Kaplan
Subject: Permission to Use Paper in Thesis

Hello Everyone,

I hope you are doing well.

I am currently preparing my PhD dissertation document and require your permission to include our publication (Depression in Epilepsy: A Systematic Review and Meta-Analysis, published in Neurology in 2013, Issue 80, Volume 6, Pages 590-599) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest
Subject: Re: Permission to Use Paper in Thesis
Date: Tuesday, 11 March, 2014 9:43:09 AM Mountain Daylight Time
From: Kirsten Fiest
To: Jonathan Dykeman

From: Jonathan Dykeman
Date: Wednesday, 5 March, 2014 1:24 PM
To: Kirsten Fiest
Subject: Re: Permission to Use Paper in Thesis

Hello,


Jonathan Dykeman

On Wed, Mar 5, 2014 at 1:22 PM, Kirsten Fiest wrote:

Hello Everyone,

I hope you are doing well.

I am currently preparing my PhD dissertation document and require your permission to include our publication (Depression in Epilepsy: A Systematic Review and Meta-Analysis, published in Neurology in 2013, Issue 80, Volume 6, Pages 590-599) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca) according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 11.

Thank you very much.

Kirsten Fiest
Subject: RE: Permission to Use Paper in Thesis

From: Nathalie Jette

To: Kirsten Fiest

I agree.

Nathalie

Nathalie Jette MD, MSC, FRCPC
Canada Research Chair in Neurological Health Services Research
AIHS Population Health Investigator
Associate Professor Neurology and
Community Health Sciences
Hotchkiss Brain Institute
Institute for Public Health

This email server has been blocking emails from outside sources recently - if you are sending an important document, please email it to this address and to nanjette@uottawa.ca. Thank you and I apologize for the inconvenience.

From: Kirsten Fiest

Sent: March 6, 2014 1:22 PM

To: Scott Patton; caswica; Contact; Colleen Maxwell; Andrew G.M. Bulloch; Nathalie Jette; Gil Kaplan; UofC

Subject: Permission to Use Paper in Thesis

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I am currently preparing my PhD dissertation document and require your permission to include our publication (Depression in Epilepsy: A Systematic Review and Meta-Analysis, published in Neurology in 2013, Issue 80, Volume 6, Pages 990-999) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertation program.

The title of my thesis is Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest

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Subject: RE: Permission to Use Paper in Thesis
Date: Wednesday, 5 March, 2014 1:57:49 PM Mountain Standard Time
From: Gilaad G. Kaplan
To: Kirsten Fiest, Scott B. Patten, Samuel Wiebe, Colleen Maxwell, Andrew G.M. Bulloch, Nathalie Jette,

You have my permission.
Gilk

From: Kirsten Fiest
Sent: Wednesday, March 05, 2014 1:22 PM
To: Scott B. Patten; Samuel Wiebe; Colleen Maxwell; Andrew G.M. Bulloch; Nathalie Jette; Gilaad G. Kaplan
Subject: Permission to Use Paper in Thesis

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In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest
Subject: Re: Permission to Use Paper in Thesis  
Date:       Wednesday, 5 March, 2014 2:32:24 PM Mountain Standard Time  
From:      Colleen Maxwell  
To:        Kirsten Fiest

Hello Kirsten,

Of course - I approve.

Colleen

On Mar 5, 2014, at 3:23 PM, "Kirsten Fiest" <kirsten.fiest@uwinnipeg.ca> wrote:

Hello Everyone,

I hope you are doing well.

I am currently preparing my PhD dissertation document and require your permission to include our publication (Depression in Epilepsy: A Systematic Review and Meta-Analysis, published in Neurology in 2013, Issue 80, Volume 6, Pages 590-599) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest
Subject: Re: Permission to Use Paper in Thesis
Date: Wednesday, 5 March, 2014 2:21:16 PM Mountain Standard Time
From: Samuel Wiebe (sent by rachtsdflskfljkl)
To: Kirsten Fiest

permission granted

SW

On Wed, Mar 5, 2014 at 1:22 PM, Kirsten Fiest wrote:

Hello Everyone,

I hope you are doing well.

I am currently preparing my PhD dissertation document and require your permission to include our publication (Depression in Epilepsy: A Systematic Review and Meta-Analysis, published in Neurology in 2013, Issue 80, Volume 6, Pages 590-599) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest

---

Samuel Wiebe MD, MSc, FRCPC, FCAHS
Associate Dean - Clinical Research
Faculty of Medicine
University of Calgary
Subject: Re: Permission to Use Paper in Thesis

Date: Wednesday, 5 March, 2014 1:36:19 PM Mountain Standard Time

From: Scott B. Patten
To: Kirsten Fiest

I agree.

Scott Patten

From: Kirsten Fiest
Sent: Wednesday, March 5, 2014 1:23 PM
To: Scott B. Patten; Samuel Wiebe; Colleen Maxwell; Andrew G.M. Bulloch; Nathalie Jette; Gilaad G. Kaplan
Subject: Permission to Use Paper in Thesis

Hello Everyone,

I hope you are doing well.

I am currently preparing my PhD dissertation document and require your permission to include our publication (Depression in Epilepsy: A Systematic Review and Meta-Analysis, published in Neurology in 2013, Issue 80, Volume 6, Pages 590-599) in my thesis.

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The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest
Appendix G: Permissions from Co-authors for Paper 2

From: Andrew G.M. Bulloch
Subject: RE: Permission to Use Paper in Thesis
Date: March 6, 2014 at 8:52 PM
To: Kirsten Piest

Permission granted Kirsten

Andy

Andrew G.M. Bulloch, PhD
Professor

From: Kirsten Piest
Sent: March 06-14 4:59 PM
To: Andrew G.M. Bulloch
Subject: Fwd: Permission to Use Paper in Thesis

Sorry to bother you Andy, but I also require your permission for this paper as well.

Thanks!

Kirsten

Begin forwarded message:

From: Kirsten Piest
Subject: Permission to Use Paper in Thesis
Date: March 5, 2014 9:48 PM MST
To: Andrew G.M. Bulloch

Hello Everyone,

Please excuse the repeat emails! Please respond to each email separately, as permission for each paper is required.

I am currently preparing my PhD dissertation document and require your permission to include our prepared and ready to submit publication (Screening Tools for Depression in Epilepsy) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Piest
Subject: RE: Permission to Use Paper in Thesis
Date: Wednesday, 5 March, 2014 1:41:50 PM Mountain Standard Time

From: Nathalie Jette
To: Kirsten Fiest

I agree.

Nathalie

Nathalie Jette RN, MSc, FRCNP
Canada Research Chair in Neurological Health Services Research
All-Health Population Health Investigator
Associate Professor Neurology and Community Health Sciences
Hotchkiss Brain Institute
Institute for Public Health
University of Calgary

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This email server has been blocking emails from outside sources recently - if you are sending an important document, please email it to this address and to: Thank you and I apologize for the inconvenience.

From: Kirsten Fiest
Sent: March 5, 2014 1:24 PM
To: Scott Patton; Nathalie Jette; Andrew G.M. Bulloch; zawiesa - Contact; Colleen Macwell

Subject: Permission to Use Paper in Thesis

Hello Everyone,

Please ensure the report emailed. Please respond to each email separately, as permission for each paper is required.

I am currently preparing my PNP dissertation document and require your permission to include our prepared and ready to submit publication (Screening Tool for Depression in Epilepsy) in my thesis.

In addition to agreeing for me to include this paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest

This message and any attached documents are only for the use of the intended recipient(s), are confidential and may contain privileged information. Any unauthorized review, use, retransmission, or other disclosure is strictly prohibited. If you have received this message in error, please notify the sender immediately, and then delete the original message. Thank you.
From: Colleen Maxwell
Subject: Re: Permission to Use Paper in Thesis
Date: March 5, 2014 at 2:42 PM
To: Kristen Fiest

Yes I approve Kristen.

Thx
Colleen

On Mar 5, 2014, at 3:40 PM, "Kristen Fiest" wrote:

Hello Everyone,

Please excuse the repeat emails! Please respond to each email separately, as permission for each paper is required.

I am currently preparing my PhD dissertation document and require your permission to include our prepared and ready to submit publication (Screening Tools for Depression in Epilepsy) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kristen Fiest
Scott B. Patten

Subject: Re: Permission to Use Paper in Thesis
Date: Wednesday, 5 March, 2014 1:35:26 PM Mountain Standard Time
From: Scott B. Patten
To: Kirsten Fiest

I agree.

Scott Patten

From: Kirsten Fiest
Sent: Wednesday, March 5, 2014 1:24 PM
To: Scott B. Patten; Nathalie Jette; Andrew G.M. Bulloch; Samuel Wiebe; Colleen Maxwell
Subject: Permission to Use Paper in Thesis

Hello Everyone,

Please excuse the repeat emails! Please respond to each email separately, as permission for each paper is required.

I am currently preparing my PhD dissertation document and require your permission to include our prepared and ready to submit publication (Screening Tools for Depression in Epilepsy) in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault ([http://theses.ucalgary.ca](http://theses.ucalgary.ca)), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.

Kirsten Fiest
From: Samuel Wiebe
Subject: Re: Permission to Use Paper in Thesis
Date: March 6, 2014 at 5:07 PM
To: Kirsten Fiest

You have my permission for this paper as well.

S Wiebe

On Thu, Mar 6, 2014 at 4:39 PM, Kirsten Fiest wrote:

Sorry to bother you Sam, but I also require your permission for this paper as well.

Thanks!
Kirsten

Begin forwarded message:

From: Kirsten Fiest
Subject: Permission to Use Paper in Thesis
Date: March 5, 2014 at 1:24:38 PM MST
To: "Scott Patten, Bulloch"

Hello Everyone,

Please excuse the repeat emails! Please respond to each email separately, as permission for each paper is required.

I am currently preparing my PhD dissertation document and require your permission to include our prepared and ready to submit publication [Screening Tools for Depression in Epilepsy] in my thesis.

In addition to agreeing for me to include the paper in my thesis, you will also be agreeing for it to be submitted to the University of Calgary Thesis Vault (http://theses.ucalgary.ca), according to the Faculty of Graduate Studies electronic thesis and dissertations program.

The title of my thesis is: Depression in Epilepsy.

Please respond to this email stating your agreement by no later than March 31.

Thank you very much.
Kirsten Fiest