Pharmacological Treatments for Problem Gambling

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Treatments for Problem Gambling

- Pathological, problem, and now disordered gambling is a significant public health and personal issue world-wide.
- Typically, CBT-based interventions are used in the treatment of problem gambling.
- These are tailored to the individual where the therapist or programmed manual delivers treatment for identified issues
- Other treatment orientations also use tailored approaches that attempt to define the precise nature of the causes or precipitating triggers of the problematic gambling (e.g., functional analysis, recalling memories, describing specific issues etc.)

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Pharmacological Treatments

- Although CBT-based interventions are more often used, and are considered to have greater evidence for their effectiveness than pharmacological interventions, there is some evidence for pharmacological treatment efficacy (Problem Gambling Research and Treatment Centre, 2011).
- Typically, systematic reviews have found opioid antagonists (simplified version; drugs that bind to opioid receptors but not activate the receptor, effectively preventing the receptor responding to opiates; e.g., naltrexone and nalmefene) have some treatment efficacy (van den Brink, 2012; Grant et al., 2012).
- Other pharmacotherapies report in-consistent efficacy; antidepressants, mood stabilisers, antipsychotics, anticonvulsants, and glutamatergic medications (Achab & Khazaal, 2011).

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Problem Gambling Research and Treatment Centre (2011) Guideline for screening, assessment and treatment in problem gambling.

Evidence-Based Recommendation 7	
Naltrexone could be used to reduce gambling severity in people with gambling problems.	C
Practice Point	
Where naltrexone is to be prescribed, the following could be considered: ▪ That naltrexone does not (at the time of reporting) have problem gambling as a registered indication so this indication would not receive Pharmaceutical Benefits Scheme (PBS) subsidy ▪ That the prescribing practitioner has the appropriate skills and training ▪ Recommended contraindications are carefully studied before prescription	

Please note the recommendations relating to pharmacological interventions described in this guideline should be applied with caution and with careful consideration to individual patient's needs.

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Opioid Antagonists

- Opioid antagonists are thought to modulate the dopaminergic transmission in the mesolimbic pathway (Grant et al., 2012).
- Naltrexone has been approved for treatment of alcohol dependence and opioid dependence by the FDA. The main effect appears to be a reduction in the pleasurable effects from drinking alcohol and for some the euphoria and craving for opiates.
- There are side effects from taking Naltrexone including nausea, dizziness, and fatigue. Other side effects include headaches, anxiety, and sleeplessness.
- The major issue is that Naltrexone is unsuitable for those with liver damage or are liable to hepatotoxicity.

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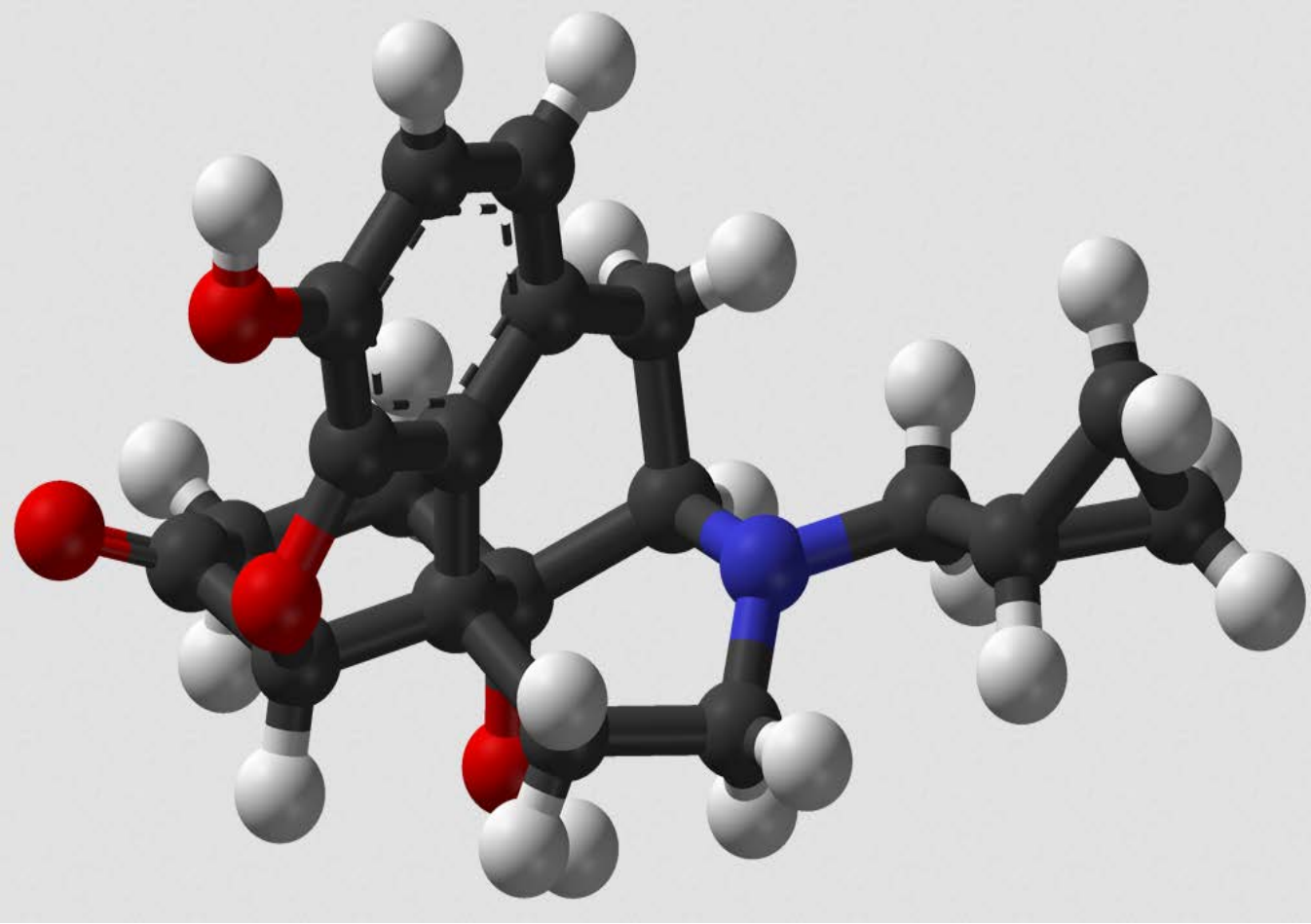
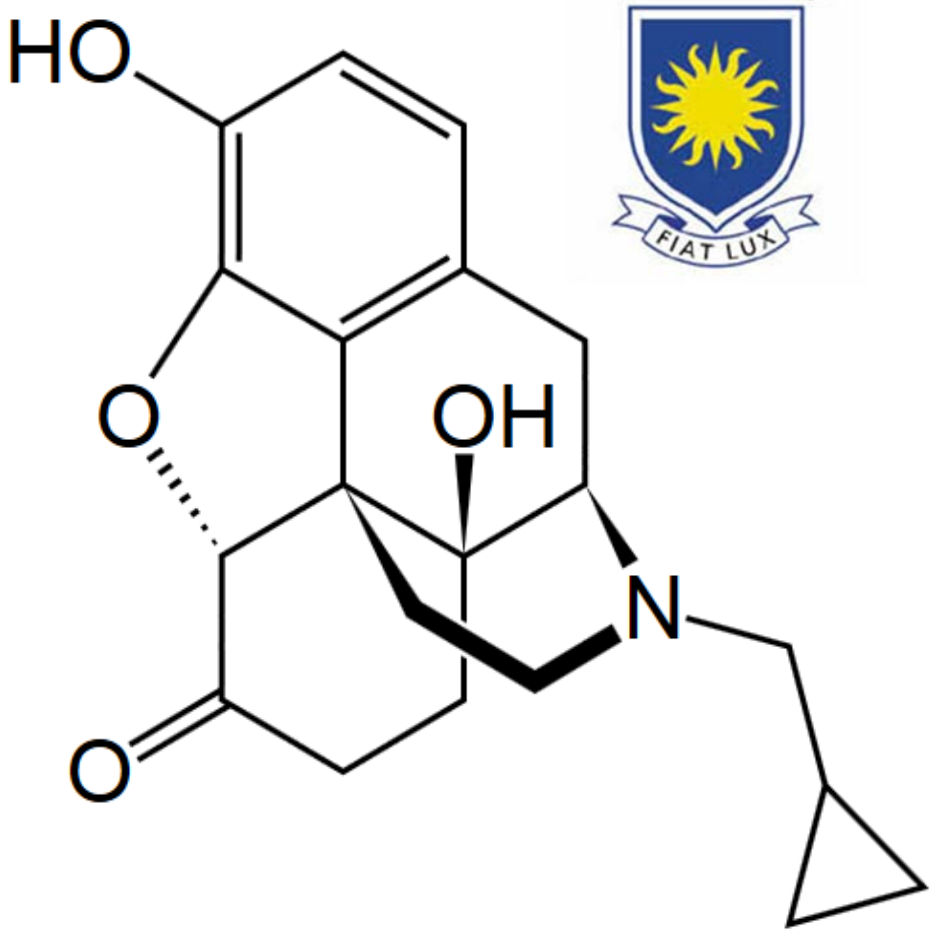
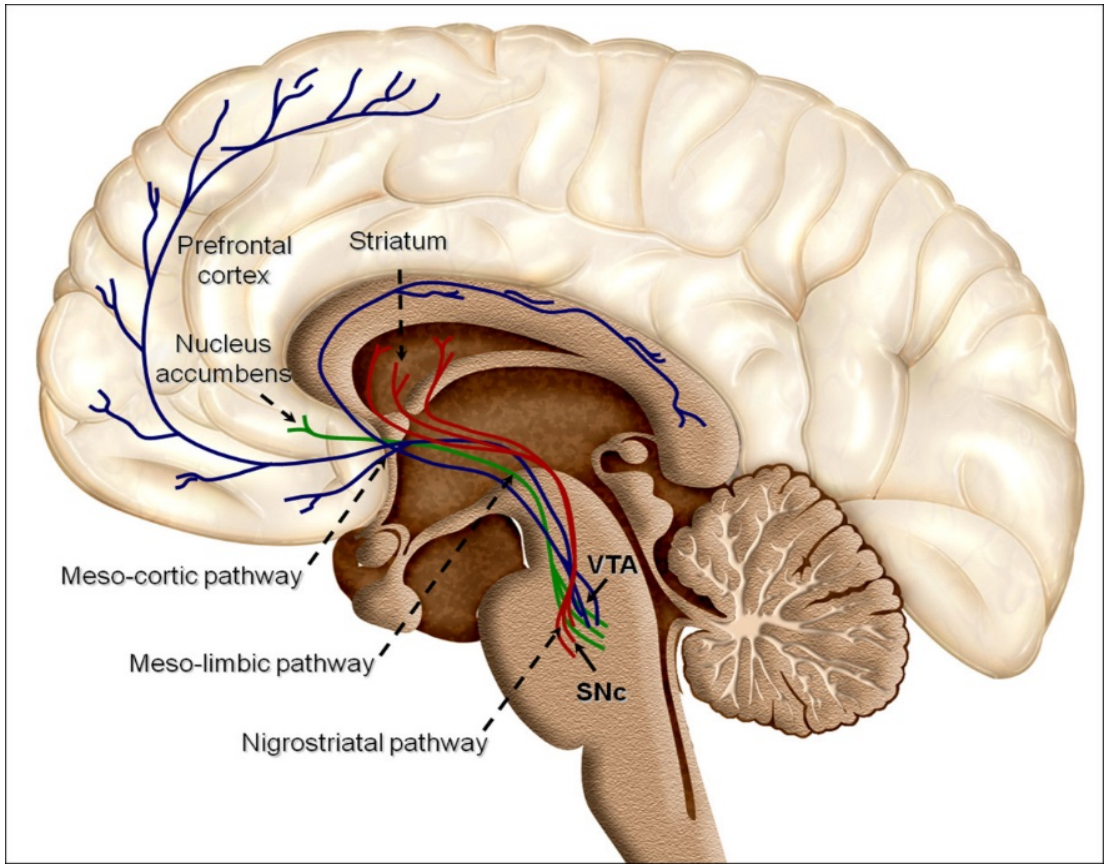




Wikipedia: Naltrexone $C_{20}H_{23}NO_4$



Arias-Carrión *et al. International Archives of Medicine* 2010
3:24 doi:10.1186/1755-7682-3-24

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Opioid antagonists

- Double-blind, placebo-controlled studies using Naltrexone or Nalmefene are generally reported to improve clinical outcome (less gambling urge, gambling abstinence).
- However, effects appear to be idiosyncratically dose related, and also there appears to be significant study drop-out and that a number of participants fail to complete the final titration of medication for at least one week.
- Participant allocation and analytical issues.

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Reference	Medication	Design/duration	Subjects	Mean daily dose (±SD)	Strengths; weaknesses	Outcome
Antidepressants						
Kim *et al.* [26]	Paroxetine	Parallel design 8 weeks with 1 week placebo lead-in	53 enrolled; 41 completers	51.7 ± 13.1 mg	Only one subject dropped out due to an adverse event; excluded Axis I disorders and atypical gender distribution of PG	Paroxetine group significantly improved compared with placebo
Grant *et al.* [27]	Paroxetine	Parallel design 16 weeks	76 enrolled; 45 completers	50 ± 8.3 mg	Multisite study; significant baseline differences between treatment groups and exclusion of Axis I disorders	Paroxetine and placebo groups with comparable improvement
Hollander *et al.* [28]	Fluvoxamine	Crossover 16 weeks with a 1 week placebo lead-in	15 enrolled; 10 completers	195 ± 50 mg	First randomized trial of fluvoxamine; excluded drug or alcohol abuse and high early placebo effect	Fluvoxamine superior to placebo
Blanco *et al.* [29]	Fluvoxamine	Parallel design 6 months	32 enrolled; 13 completers	200 mg	6 month study duration; small sample size	Fluvoxamine not statistically significant from placebo
Sáiz-Ruiz *et al.* [31]	Sertraline	Parallel design 6 months	60 enrolled; 44 completers	95 mg	6 month study duration; high placebo response rate	Similar improvement in both groups
Black *et al.* [32]	Bupropion	Parallel design 12 weeks	39 enrolled; 22 completers	324 mg	Only trial of a non-SSRI antidepressant; small sample size	No difference between groups on any measure
Opioid antagonists						
Kim *et al.* [19]	Naltrexone	Parallel design 12 weeks with 1 week placebo lead-in	89 enrolled; 45 completers	188 ± 96 mg	First systematic investigation of naltrexone; atypical gender distribution of PG	Naltrexone group improved significantly compared with placebo
Grant *et al.* [33]	Naltrexone	Parallel design 18 weeks	77 enrolled; 49 completers	Fixed dose (50 mg, 100 mg, 150 mg)	Longest PG trial investigating naltrexone; excluded bipolar disorder and substance use disorders	Naltrexone group improved significantly compared with placebo
Toneatto *et al.* [34]	Naltrexone	11 weeks with cognitive behavioural therapy (CBT)	52 enrolled; 38 completers	100 ± 59 mg	Sample included co-current alcohol use disorder; no control group and small sample size	Naltrexone plus CBT and placebo plus CBT both improved
Grant *et al.* [35]	Nalmefene	Parallel design 16 weeks	207 enrolled; 73 completers	Fixed dose study (25 mg, 50 mg, 100 mg)	Large sample size; excluded bipolar disorder and substance use disorders	Nalmefene 25 mg and 50 mg significantly improved compared with placebo
Grant *et al.* [36]	Nalmefene	Parallel design 16 weeks with 1 week placebo lead-in	233 enrolled; 126 completers	Fixed dose study (20 mg, 40 mg)	Large sample size; current Axis I disorders and individuals seeking psychotherapy were excluded	intention-to-treat nalmefene no different from placebo. *Post hoc* analyses: 40 mg nalmefene significant improvement on primary measure.

Systematic Review and Meta-Analysis

- However, a very recent systematic review of RCTs (with placebo comparison) examining pathological gambling with no co-morbidities have challenged the efficacy of opioid antagonists and suggest their effectiveness was significantly related to non-adherence to intention to treat (ITT) analytical principles (Bartley & Bloch, 2013).
- This results suggests that these effects were due not to the efficacy of the treatment but to the efficacy for those who received Treatment (i.e., attrition effects).

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Table 1. Characteristics of included trials.

Study	Medication	N (number of participants)	Length of trial (in weeks)	Primary outcome measure	Method of analysis	Proportion of subjects included in analysis
Opiate antagonists						
Kim 2001	Naltrexone	83	18 (1 week placebo lead-in)	PG-CGI[2], G-SAS[4]	Not-ITT	43%
Grant 2006	Nalmefene	207	16	PG-YBOCS[1]	Not-ITT	71%
Grant 2008	Naltrexone	77	18	PG-YBOCS[1]	ITT	100%
Toneatto 2009	Naltrexone	52	11	Gambling Frequency	ITT	100%
Grant 2010	Nalmefene	233	3	PG-YBOCS[1]	Modified-ITT	84%
Antidepressants						
Hollander 2000	Fluvoxamine	15	16 weeks (two 8 week crossover phases)	PG-YBOCS[1], PG-CGI[2]	Not-ITT	67%
Blanco 2002	Fluvoxamine	32	6 months	Amt. of money spent gambling/ wk	Not-ITT	41%
Kim 2002	Paroxetine	45	8 (1 week placebo lead-in)	G-SAS[4]	ITT	100%
Grant 2003	Paroxetine	76	16	CGI[3], PG-YBOCS[1]	ITT	100%
Saiz-Ruiz 2005	Sertraline	60	24	CCPGQ[5]	ITT	100%
Black 2007	Bupropion (Antidepressant)	39	12	PG-YBOCS[1]	ITT	100%
Antipsychotics						
Fong 2008	Olanzapine	21	7	PG-CGI[2]	Not-ITT	91%
McElroy 2008	Olanzapine	42	12	PG-YBOCS[1]	ITT	100%
Other						
Berlin 2011	Topiramate	42	14	PG-YBOCS[1]	ITT	100%

[1]Pathological Gambling Adaptation of Yale-Brown Obsessive-Compulsive Scale, [2]Clinical Global Impression for Pathological Gambling, [3]Clinical Global Impression Scale, [4]Gambling Symptom Assessment Scale, [5]Criteria for Control of Pathological Gambling Questionnaire

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Study	SMD (95% CI)	Relative weight
Kim 2001	1.506 (.751–2.261)	6.31
Grant 2006	0.516 (.152–.881)	27.06
Grant 2008	.380 (-.142–0.902)	13.22
Toneatto	.054 (-.490–.598)	12.14
Grant 2010	-.178 (.028–.408)	41.27
Overall	**0.183 (-.058–0.423)**	
Fixed-effect model	Heterogeneity	
Z = 2.253 p < 0.05	I^2 = 0.00 P = 0.56	

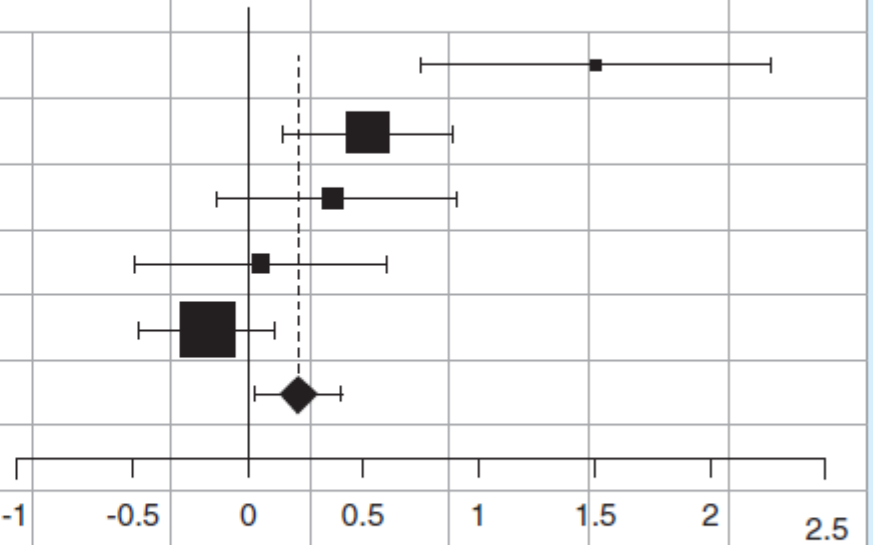

Figure 2. Opiate antagonist forest plot.

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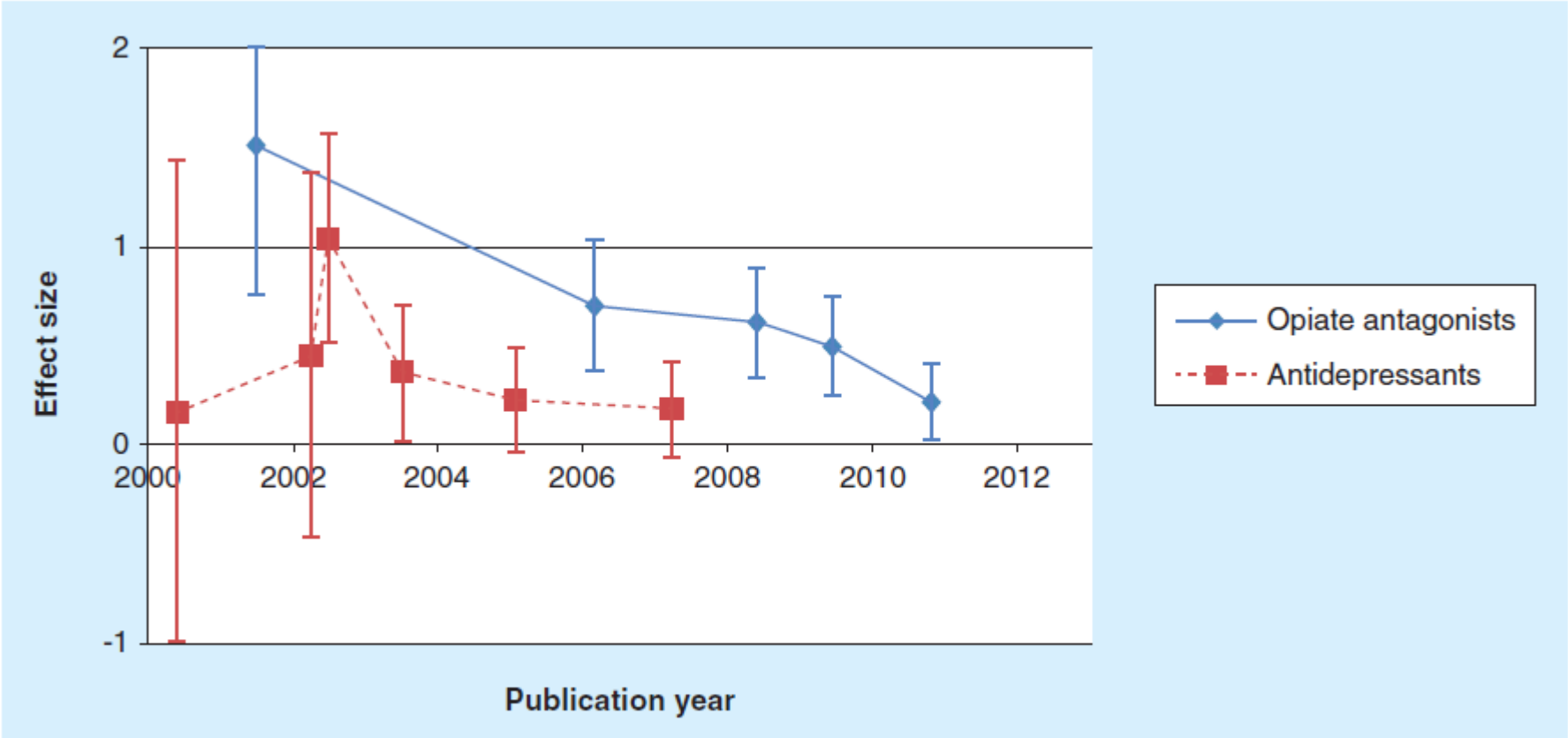

Figure 4. Efficacy of opioid antagonists by year of trial publication.

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Trial Heterogeneity

- There appears significant between trial heterogeneity in outcomes (i.e., differences between study effect sizes, and between study total variance).
- There was also significant variability between studies in study methodologies (both positive and negative reviews); dosages, number of participants, reported co-morbidities, concurrent treatment, gender distributions, type and inclusion of personality disorders and axis I disorders, and length of trail, and follow-up.
- There also appears an effect by publication year.

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Tailored Pharmacological Interventions

- Pharmacological Interventions, like psychosocial interventions, may be more efficacious if they were tailored to particular clustering of symptoms and biological sensitivities.
- For example, in other addiction related disorders, sub-typing based on severity, where psycho-social interventions are ineffective for changing behaviour (e.g., some cases of alcohol consumption), regularly use multiple medications to arrest primary and secondary symptoms.
- For example, Naltrexone is often used as the 'first line' medication for moderate to severe alcohol dependence to reduce craving, and other medications, such as diazepam, are also used to attenuate other symptoms (e.g., withdrawal).

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Co-morbidities: Prevalence

- Problematic gambling is often associated with high rates of other comorbid disorders (Lorains et al., 2011; systematic review of general population reports using randomized sampling measures).
- Highest mean prevalence was for nicotine dependence (60.1%), followed by any substance use disorder (57.5%), any type of mood disorder (37.9%) and any type of anxiety disorder (37.4%).
- However, there was evidence of moderate heterogeneity across studies. suggesting that rate estimates do not necessarily converge around a single population figure, and that weighted means should be 'interpreted with caution'.

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Co-morbidities: Treatment Seeking

- Problematic gambling is also associated with high rates of comorbid personality disorders (Dowling et al., under-review Journal of Personality Disorders; systematic review of treatment seeking reports).
- Almost one-half (47.9%) of treatment seeking problem and pathological gamblers displayed comorbid personality disorders (DSM-IV; Axis II). They were most likely to display Cluster B disorders (dramatic; 17.6%), with smaller proportions reporting Cluster C disorders (anxious; 12.6%) and Cluster A disorders (odd; 6.1%).
- The most prevalent personality disorders were narcissistic (16.6%), antisocial (14.0%), avoidant (13.4%), obsessive-compulsive (13.4%), and borderline (13.1%) personality disorders.
- Even higher levels of heterogeneity were observed in the meta-analysis of treatment seekers.

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Table 3
Prevalence of comorbid Cluster A personality disorders in treatment-seeking problem and pathological gambling

Study	Comorbidity measure	Any Cluster A disorder	Paranoid personality disorder	Schizoid personality disorder	Schizotypal personality disorder
Blaszczynski & Steel (1998)	PDQ-R [a]		40.2%	20.7%	37.8%
Echeburua & Fernandez-Montalvo (2008)	IPDE [b]		8.0%	0%	0%
Echeburua & Fernandez-Montalvo (2008)	MCMI-II [c]		8.0%	0%	0%
Jimenez-Murcia et al. (2009)	SCID (DSM-IV) [d]	2.2%			
Kerber et al. (2008)	PDQ-4 [e]		10.0%	15.0%	7.5%
Kroeber (1992)	Clinical diagnosis (DSM-III-R)		9.3%	9.3%	
Kruedelbach et al. (2006)	SCID (DSM-III-R) [f]	4.3%	2.5%	1.2%	1.2%
Pelletier et al. (2008)	SCID (DSM-IV) [d]	24.0%	18.0%	4.0%	3.0%
Specker et al. (1996)	SCID (DSM-III-R) [f]	5.0%	2.5%	2.5%	0%
Summary effect (95% CI)		6.1% (1.5-22.1)	10.1% (4.2-22.1)	6.0% (2.5-13.7)	4.1% (0.8-19.4)
I^2 (%)		94.33	88.94	79.18	91.49

[a] PDQ-R: Personality Disorder Questionnaire-Revised; [b] IPDE: International Personality Disorders Examination; [c] MCMI-II: Millon Clinical Multiaxial Inventory-II; [d] SCID (DSM-IV): Structured Clinical Interview for DSM-IV; [e] PDQ-4: Personality Disorder Questionnaire-4; [f] SCID (DSM-III-R): Structured Clinical Interview for DSM-III-R

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Table 4
Prevalence of comorbid Cluster B personality disorders in treatment-seeking problem and pathological gambling

Study	Comorbidity measure	Any Cluster B disorder	Antisocial personality disorder	Borderline personality disorder	Histrionic personality disorder	Narcissistic personality disorder
Blaszczynski & McConaghy (1994)	DSM-III checklist for APD [a]		15.4%			
Blaszczynski & Steel (1998)	PDQ-R [b]		29.3%	69.5%	65.9%	57.3%
Echeburua & Fernandez-Montalvo (2008)	IPDE [c]		8.0%	16.0%	0%	8.0%
Echeburua & Fernandez-Montalvo (2008)	MCMI-II [d]		16.0%	0%	0%	32.0%
Grall-Bronnec et al. (2011)	MINI [e]		4.9%			
Ibanez et al. (2001)	SCID (DSM-III-R) [f]		14.5%			
Jimenez-Murcia et al. (2009)	SCID (DSM-IV) [g]	6.5%				
Kerber et al. (2008)	PDQ-4 [h]		7.5%	10.0%	12.5%	17.5%
Kroeber (1992)	Clinical diagnosis (DSM-III-R)		20.9%	4.7%		11.6%
Kruedelbach et al. (2006)	SCID (DSM-III-R) [f]	30.2%	9.9%	11.7%	6.8%	18.5%
Ledgerwood & Petry (2010)	SCID (DSM-IV) [g]		15.3%			
Pelletier et al. (2008)	SCID (DSM-IV) [g]	42.0%	29.0%	10.0%	1.0%	15.0%
Petry et al. (2005)	SCID (DSM-III-R) [f]		7.4%			
Pietrzak & Petry (2005)	SCID (DSM-IV) [g]		16.5%			
Specker et al. (1996)	SCID (DSM-III-R) [f]	7.5%	0%	2.5%	0%	5.0%
Summary effect (95% CI)		17.6% (6.0-41.8)	14.0% (10.5-18.4)	13.1% (4.3-33.5)	6.3% (1.0-30.4)	16.6% (8.0-31.2)
I^2 (%)		96.72	76.11	94.48	95.29	90.84

[a] DSM-III checklist for APD: DSM-III checklist for Antisocial Personality Disorder; [b] PDQ-R: Personality Disorder Questionnaire-Revised; [c] IPDE: International Personality Disorders Examination; [d] MCMI-II: Millon Clinical Multiaxial Inventory-II; [e] MINI: Mini International Neuropsychiatric Interview; [f] SCID (DSM-III-R): Structured Clinical Interview for DSM-III-R; [g] SCID (DSM-IV): Structured Clinical Interview for DSM-IV; [h] PDQ-4: Personality Disorder Questionnaire-4

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Table 5
Prevalence of comorbid Cluster C personality disorders in treatment-seeking problem and pathological gambling

Study	Comorbidity measure	Any Cluster C disorder	Avoidant personality disorder	Dependent personality disorder	Obsessive-Compulsive personality disorder
(Blaszczynski & Steel, 1998)	PDQ-R [a]		36.6%	48.8%	31.7%
(Echeburua & Fernandez-Montalvo, 2008)	IPDE [b]		0%	0%	0%
(Echeburua & Fernandez-Montalvo, 2008)	MCMI-II [c]			8.0%	
(Jimenez-Murcia et al., 2009)	SCID (DSM-IV) [d]	3.7%			
(Kerber et al., 2008)	PDQ-4 [e]		27.5%	5.0%	37.5%
(Kroeber, 1992)	Clinical diagnosis (DSM-III-R)			7.0%	
(Kruedelbach et al., 2006)	SCID (DSM-III-R) [f]	13.0%	6.2%	3.1%	5.6%
(Pelletier et al., 2008)	SCID (DSM-IV) [d]	27.0%	10.0%	3.0%	16.0%
(Specker et al., 1996)	SCID (DSM-III-R) [f]	17.5%	12.5%	5.0%	5.0%
Summary effect (95% CI)		12.6% (4.8-29.1)	13.4% (5.9-27.5)	6.0% (1.4-22.5)	13.4% (5.9-27.5)
I^2 (%)		93.94	88.49	93.21	88.24

[a] PDQ-R: Personality Disorder Questionnaire-Revised; [b] IPDE: International Personality Disorders Examination; [c] MCMI-II: Millon Clinical Multiaxial Inventory-II; [d] SCID (DSM-IV): Structured Clinical Interview for DSM-IV; [e] PDQ-4: Personality Disorder Questionnaire-4; [f] SCID (DSM-III-R): Structured Clinical Interview for DSM-III-R

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Pathways

- Theoretical and some empirical work suggests that there are separate but related pathways to problematic gambling (e.g., Pathways Model; Blaszczynski & Nower, 2002; Gupta et al., 2013).
- This work suggests that different treatment approaches are likely, and have implication for pharmacological interventions.
- For example, the 'Pathways Model' suggests that a sub-type of gamblers have a combination of conditioned, mood, and personality disordered characteristics (i.e., Pathway 3). These gamblers are likely to require a combination of interventions including possibly mood and personality medications.

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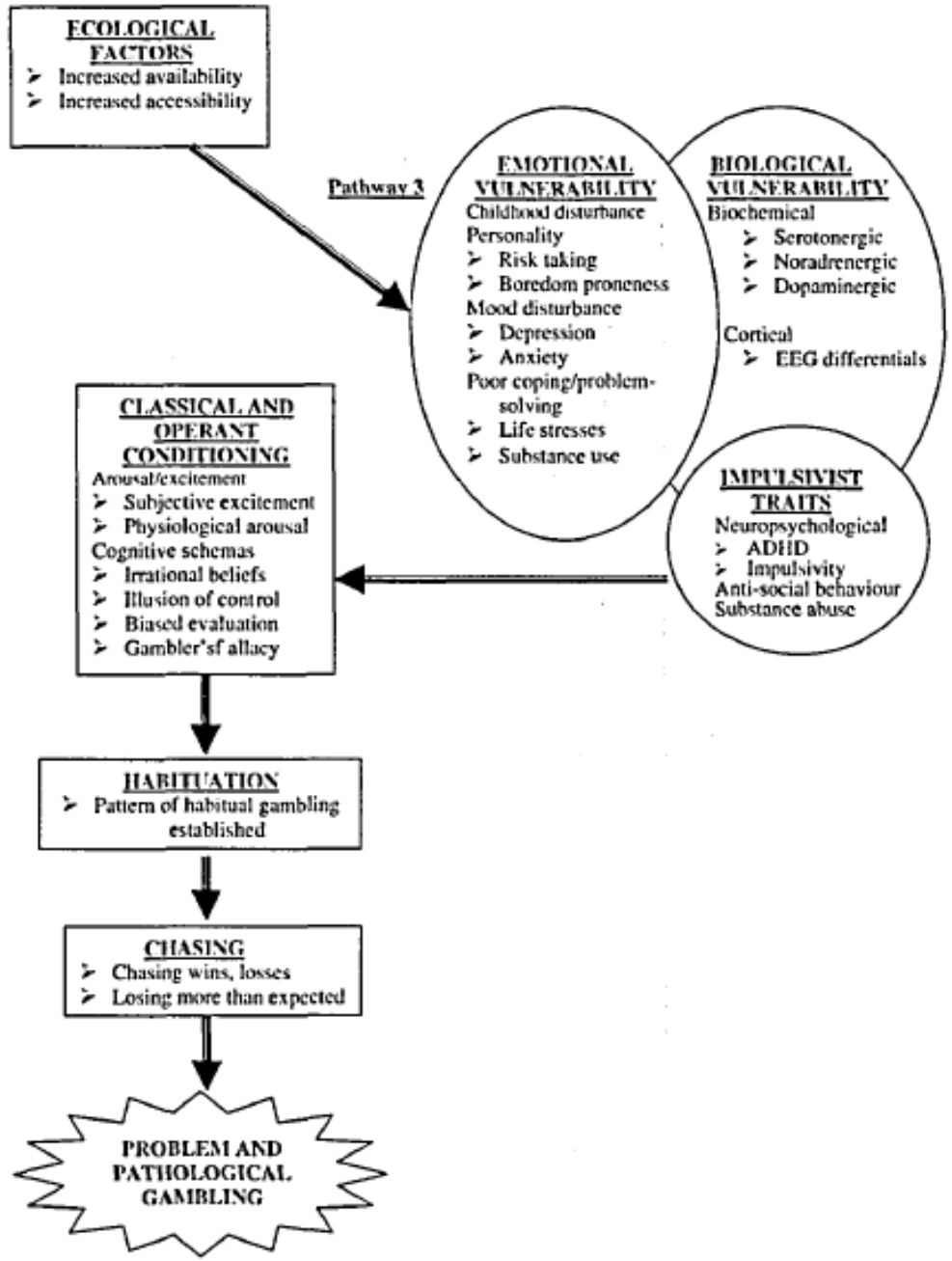

Figure 3 Integrated model of problem gambling, Pathway 3

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Hierarchies

- Recently, new research has been published that appears to show gambling symptoms cluster in apparent increasing levels of severity.
- Christensen et al. (2014) found DSM-IV criteria in a treatment seeking population appeared to follow the progression similar to substance dependence; 1) some experimentation, 2) development of a problem (including the hallmark biological criteria of tolerance and withdrawal), and 3) problems for the gambler, their associates, and society.
- The clustering of criteria also suggest distinct experiences of harm as severity increases, and possibly different biological mechanisms at different levels.

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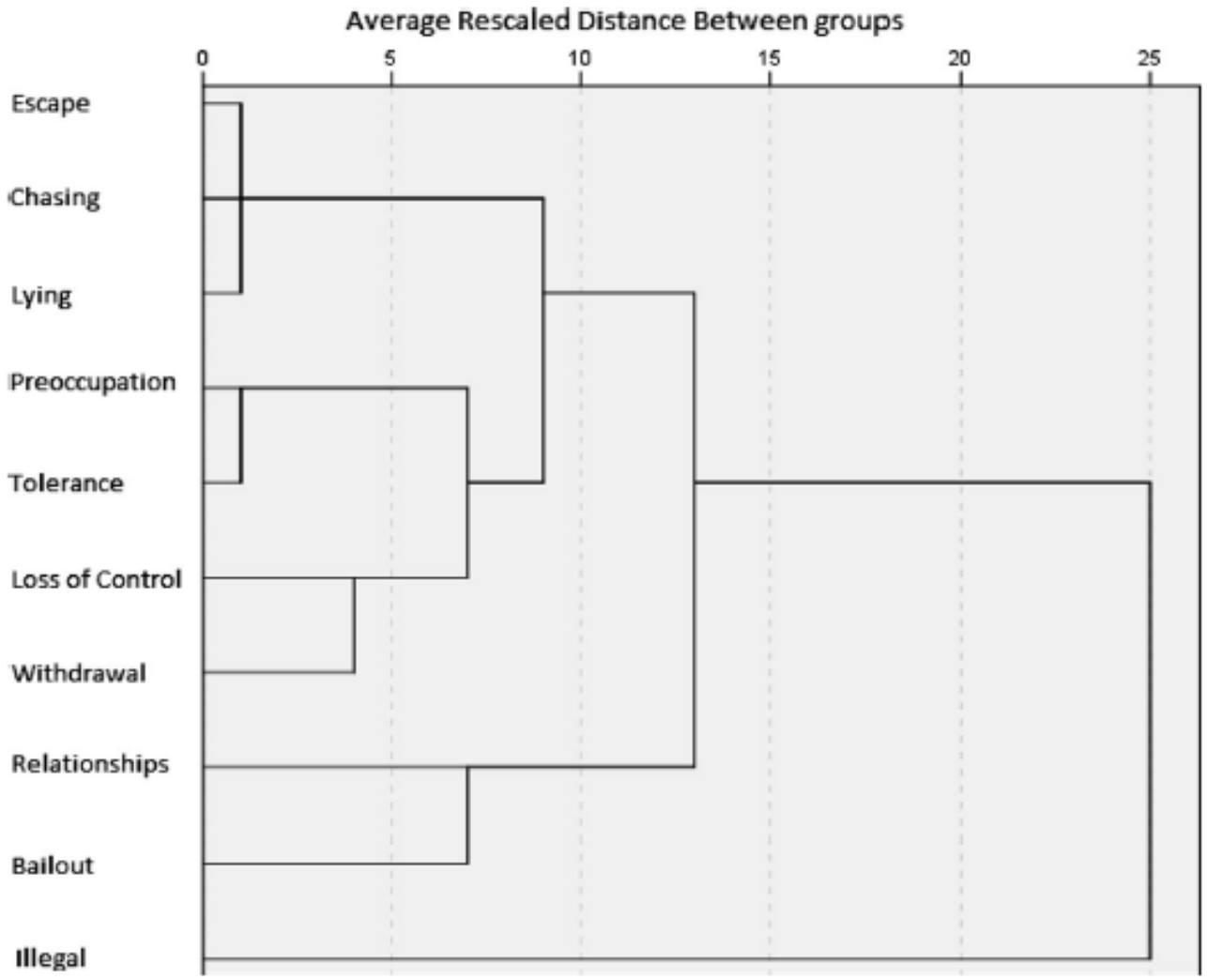

Fig. 2 Dendrogram

Sub-types and pharmacologies

- Previous research has suggested similar strategies. Dannon et al. (2006) suggested pathological gambling was a heterogeneous disorder where sub-typing of gamblers could inform pharmacologic interventions.
- Dannon et al. proposed three sub-types based on clinical experience and partial and moderate efficacy evidence from trails of various medications.
- These were; impulsive type gamblers (young male risk takers) who may respond best to bupropion or mood stabilizers, obsessive-compulsives to SSRIs and SNRIs (which may target depressive and anxious symptoms as well as compulsive behaviour; females in mid-life experiencing trauma), and addictive subtypes (high co-morbid alcohol abuse and dependence) to Naltrexone or Nalmefene.

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Drug Actions

- Recent reviews link different neuro-chemicals to pathological gambling (See Conversano et al., 2012)
- Serotonin (5HT): linked to increased vulnerabilities towards impulsive behaviours, including *lower Serotonin 'state'* (possibly inducing craving) and *hypersensitive postsynaptic receptors*, similar to reports in obsessive-compulsive disorder. Further, other reports suggesting *rapid 5HT turn-over*, and others report lower 5HT platelet transporters in pathological gamblers.
- Norepinephrine (NE): linked to arousal and novelty seeking, pathological gamblers had higher urinary values of NE, and *increased during Pachinko playing*.

Drug Actions

- Opioids: Modulate the Dopamine pathways, where opioid receptors differentially inhibit mesolimbic neurons where an *alteration* in these receptors may contribute to the development of addiction. Similar to NE, Pachinko play induced *higher blood levels of opioid endorphins during 'high-pitched' play*.

- Stress-response system: Initiates the autonomic nervous system response to stress by the release of NE and epinephrine which modulate physiological functions like respiration and heart rate. *Cortisol levels have been found to increase* to a greater extent for pathological gamblers than controls when *wagering their own money* on real-life casino sessions of blackjack.

Sub-types and Genetics

- Some evidence suggests that familial traits or histories can influence drug receptivity in the treatment of gambling; pooled analyses of those who responded to opioid antagonists reported significant reductions in gambling urges, particularly in participants with a family history of alcohol dependence (Grant, 2009).
- Twin studies have estimated that the heritability of pathological gambling is in the range of 50-60%, and shares genetic vulnerability factors with antisocial behaviours, alcohol dependence, and major depressive disorder (Lobo & Kennedy, 2009).

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Conclusions

- Evidence of significant levels of heterogeneity across studies and within the gambling population and in treatment seekers.
- Implication that gamblers are too diverse for one single pharmacological treatment.
- Instead of theorising from related disciplines a more productive approach may be to look to find more specificity in the diagnosis and match treatments (including pharmacologies) to diagnosed issues similar to the practice in psycho-social treatment approaches.
- A consequence of this approach is that different medications (and combinations) may be appropriate for different levels of severity, comorbidities, phenomenologies, drug sensitivities, and familial histories.
- Broad systematic reviews and meta-analyses of pharmacological treatment efficacy are currently too blunt for generalising across studies without greater specificity and analysis on the demographics, histories, severities, and phenomenologies of gamblers.

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