PSYC1022: The Psychology of Addiction

Topic 14: Pharmacotherapy

Dr. Helena Pacitti

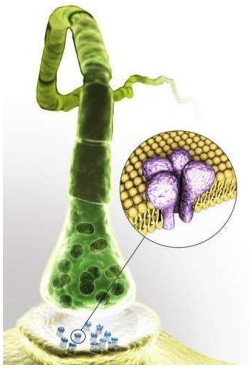
Outline:

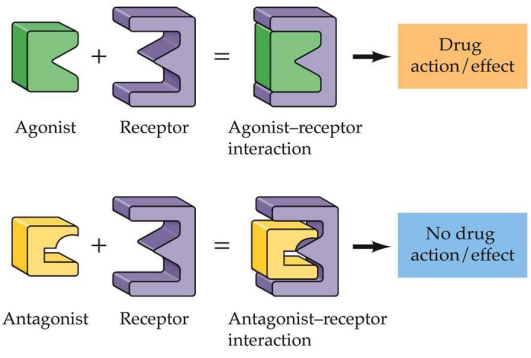
- Agonist & antagonist drugs
- Treatments for alcohol
  - Acamprosate
  - Naltrexone
  - Disulfiram
- Opiates
  - Methadone
  - Suboxone
- Nicotine
  - Nicotine replacement therapy (NRT)
  - Bupropion
  - Varenicline
- Treatments for stimulants
- Treatments for cannabis
- Cognitive enhancers

1

Agonist & antagonist drugs

Most pharmacotherapies act upon brain receptors to change activity of neurotransmitter (NT) systems.
Agonists: activate receptors to increase their function (either exciting or inhibiting the cell depending upon which ions the associated channel allows across the membrane).
Antagonists: fit a receptor imperfectly & thus block the action of the neurotransmitter that would otherwise act upon that receptor (without the antagonist having any direct effect on the channel itself)





2

Agonist & antagonist drugs

Full agonists: activate the receptor to its maximal response
Partial agonists: activates the receptor to less than its full response.

- By occupying receptors but eliciting a submaximal response, partial agonists actually function as competitive antagonists, blocking full agonists from producing a maximal response.
- This function is thought important for providing a weaker analogue of the addictive drug (to ameliorate withdrawal) while simultaneously blocking the full rewarding effect of the addictive drug.

Indirect agonists: enhance the function of NTs indirectly, without activating the receptors for that NT themselves

- e.g. by blocking transporters, inducing NT release, and/or inhibiting NT metabolism.

Therapeutics used in the treatment of addiction and their mechanism of action

Therapeutic	Drug of abuse	Mechanism of action
Acamprosate	Alcohol	Partial agonist
Buprenorphine	Opioids	Partial agonist
Bupropion	Nicotine	Indirect agonist
Methadone	Opioids	Agonist
Naloxone	Opioids	Antagonist
Naltrexone	Alcohol	Antagonist
Nicotine	Nicotine	Agonist
Varenicline	Nicotine	Partial agonist

Pierce et al. (2012)

3

Acamprosate for alcoholism

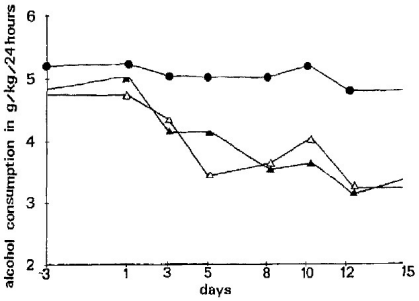
Alcohol increases the inhibitory NT GABA & decreases the excitatory NT glutamate (reduced activity across the CNS)

- Chronic occupancy of these receptors following alcohol results in downregulation & desensitisation whereby withdrawal from alcohol produces the converse changes in NT activity, producing a dangerous increase in brain excitation

Acamprosate: a GABA agonist & glutamate NMDA antagonist, can oppose the neural sequela of alcohol withdrawal

Boismare et al (1984): rats reduced alcohol consumption over 15 days given daily co-administration of Acamprosate. Controls administered placebo (circles) vs. 2 groups given different doses of Acamprosate (triangles).

- Not clear whether Acamprosate reversed withdrawal or competed with direct rewarding effects of alcohol, or both, but nevertheless, suggests efficacy as a therapeutic agent.



Boismare et al. (1984)

4

		Duration of Study / Followup (Months)	Number of Patients (N)	Acamprosate Dosage	Rate of Complete Abstinence	Percent Days Abstinent[a]	Time to First Drink
International Trials	**Country**						
Namkoong et al, 2003 [105]	South Korea	2	142	1332 or 1998 mg/day[b]	−	−	−
Lhuintre et al, 1985 [91]	France	3	85	1000–2250 mg/day[b]	+	NM	NM
Lhuintre et al, 1990[*] [92]	France	3	569	1332 mg/day	NM	NM	NM
Roussaux et al, 1996 [95]	Belgium	3	127	1332 or 1998 mg/day[b]	−	NM	NM
Pelc et al, 1997 [77]	Belgium, France	3	188	1332 or 1998 mg/day[b]	++	++	++
Baltieri et al., 2004 [107]	Brazil	3/3	75	1998 mg/day	+	NM	NM
Kiefer et al, 2003[†] [104]	Germany	3/3	160	1998 mg/day	++	NM	+
Morley et al, 2006[†] [110]	Australia	3/3	169	1998 mg/day	NM	−	−
Niederhofer, et al. 2003 [106]	Austria	3	26	1332 mg/day	++	++	NM
Pelc et al, 1992 [93]	Belgium, France	6	102	1998 mg/day	++	++	NM
Ladewig et al, 1993 [94]	Switzerland	6/6	61	1332 or 1998 mg/day[b]	+	+	NM
Geerlings et al, 1997 [98]	Netherlands, Belgium, Luxembourg	6/6	262	1332 or 1998 mg/day[b]	+	+	+
Poldrugo, 1997 [99]	Italy	6/6	246	1332 or 1998 mg/day[b]	++	++	++
Chick et al, 2000 [101]	United Kingdom	6/1	581	1998 mg/day	−	−	NM
Tempesta et al., 2000 [102]	Italy	6/3	330	1998 mg/day	++	+	++
Gual, et al.2001 [103]	Spain	6	288	1998 mg/day	+	++	NM
Paille et al, 1995 [76]	France	12/6	538	1332 or 1998 mg/day[c]	−	++	++
Sass et al, 1996 [90]	Germany	12/12	272	1332 or 1998 mg/day[b]	++	++	+
Whitworth et al, 1996 [96]	Austria	12/12	448	1332 or 1998 mg/day[b]	++	+	++
Barrias et al, 1997 [97]	Portugal	12/6	302	1332 or 1998 mg/day[b]	+	++	++
Besson et al, 1998[‡] [100]	Switzerland	12/12	110	1332 or 1998 mg/day[b]	+	+	NM
U. S. Trials							
Anton et al, 2006[†] [108]		4/12	1383	3000 mg/day	NM	−	NM
Mason et al, 2006 [109]		6/2	601	2000 or 3000 mg/day[c]	NM	+[d]	NM

Mason & Heyser (2010)

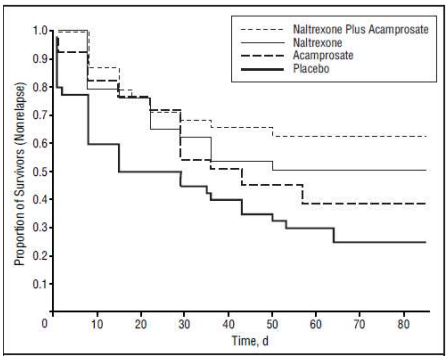
5

Naltrexone for alcoholism

Acamprosate increased abstinence rates by about 10-20% over 80 days following the quit date.

Naltrexone: antagonist of opioid receptors, which blocks the function of endogenous endorphin

- first studied for alcohol dependence in 1970s following discovery of the role of opiate receptors in opiate dependence
- Initial reports showed that Naltrexone reduced alcohol consumption in animals models & has since been shown to have clinical efficacy in humans
- Importantly, Naltrexone & Acamprosate combined produce additive treatment effects
  - suggesting these drugs have different mechanisms of action which combine to produce broader protection from relapse.



Kiefer et al. (2003)

6

Naltrexone for alcoholism

Maisel et al. (2013): found that Acamprosate increased the number of abstinent days following quitting to a greater extent than Naltrexone. However, Naltrexone reduced craving & heavy-drinking sessions whereas Acamprosate did not.

- One explanation for these data is that Acamprosate promotes abstinence by ameliorating withdrawal, whereas Naltrexone promotes abstinence by blocking the euphoric effects of alcohol consumption produced by endorphin release, thus reducing craving and heavy use following a lapse.

Outcome	*Medication*	*P*
Abstinence aggregate	Naltrexone	0.001
	Acamprosate	<0.001
Heavy drinking aggregate	Naltrexone	<0.001
	Acamprosate	0.346
Craving	Naltrexone	0.005
	Acamprosate	0.347

7

Disulfiram for Alcoholism

Disulfiram (Antabuse): blocks acetaldehyde dehydrogenase (liver enzyme that breaks down alcohol) resulting in sensitivity to alcohol consumption & an array of aversive symptoms (flushing of the skin, accelerated heart rate, shortness of breath, nausea, vomiting, throbbing headache, visual disturbance & confusion).

- The idea is not that patients will actually experience aversive symptoms & because of them extinguish alcohol use. Drinking whilst taking Disulfiram is dangerous so clients who do not understand this, or for other reasons are unable to abstain despite taking the medication are not appropriate candidates for Disulfiram therapy.
- Compliance with treatment is a major issue in using Disulfiram (i.e. people stop taking it so they can drink).
  - Attempts have been made to circumvent this using depot treatment (a technique which slows the release of Disulfiram). Unfortunately, the preparations evaluated do not maintain adequate plasma concentrations of Disulfiram.
- Recent reviews have cast serious doubt on Disulfiram's efficacy in promoting abstinence, subsequently, it is now rarely used as a treatment (Heilig & Egli 2006)

8

Methadone for opiate dependence

Methadone: opiate agonist, similar to heroin & morphine, but it has higher oral bioavailability & longer "half-life" making it useful for maintenance therapy.

- Methadone maintenance is a morally tolerable harm reduction strategy which effectively ameliorates heroin withdrawal, weaning addicts from street heroin, reducing black market distribution, overdose, poisoning from impurities & disease transmission from needle sharing.
- It is the front line pharmacotherapy for heroin addiction globally, although it is often polarizing.
- A crucial aspect of this treatment is that oral administration must be carefully supervised in-house by treatment clinics to obviate dependence which would arise from it being injected & the consequent bleeding of supply onto the streets.
- Treatment is limited by the distance to the closest clinic & the high frequency of visits required.

9

Suboxone for opiate dependence

Suboxone: a combination of Buprenorphine (partial opioid receptor agonist with good oral bioavailability) & Naloxone (opioid receptor antagonist).

- Naloxone has poor oral bioavailability so oral administration of Suboxone is effectively rewarding because the Buprenophine effect dominates.
- However, if Suboxone is injected, Naloxone counters the opioid agonist effects, so the injection is not rewarding.
- This allows addicts to take larger supplies of Suboxone home & administer it without fear of an injection high & resale.

10

Nicotine replacement

1967: Dr. Claes Lundgren suggested oral nicotine as a substitute for tobacco based on the observation that sailors sometimes switched from smoking to chewing tobacco without difficultly when assigned to submarine duty.

Ove Ferno: recognized the commercial potential of nicotine replacement & embarked on a research program to design a means to orally administer nicotine with delayed absorption.

- The result was nicotine gum.

11

Nicotine replacement for smoking

Numerous randomised clinical trials have now tested a variety of nicotine replacement products vs. placebo & found efficacy in improving abstinence following a quit attempt.

Stead et al. (2008): meta-analysis of 132 published trials. Examined quit rates at 6 month follow up.

- Overall, the risk ratio (RR of 1 equals no difference) of abstinence for any form of NRT relative to control was 1.58 (indicates that the NRT group was 58% more likely to remain abstinent than the control group).
- RRs for each type: 1.43 gum; 1.66 patch; 1.90 inhaler; 2.00 tablets/lozenges; 2.02 nasal spray.

Despite these relative improvements by NRT, absolute quit rates remain disappointly low

- between 6-16% of NRT participants remain abstinent after 6 months whereas about 2-10% of placebo participants remain abstinent.
- However, the proportion of those reducing their cigarette smoking by more than 50% at six months is 23.7% for NRT-treated patients & 13.5% for placebo-treated controls.

NRT appears to be effective at reducing the frequency with which individuals smoke, and so should be used long term until full abstinence is finally achieved (Wang et al. 2008)

12

Bupropion (Zyban) for smoking

Tobacco withdrawal syndrome is associated with a marked increase in depression & depression is linked to an inability to quit smoking. Consequently, anti-depressant agents might protect against relapse by ameliorating depression.

- Hurt et al. (1997): anti-depressant Bupropion was tested & found to produce superior quit rates compared to placebo. It was subsequently marketed as a smoking cessation agent under the name Zyban.

Bupropion: dopamine & noradrenaline indirect agonist (works as a reuptake inhibitor increasing the function of these neurotransmitters). Also an antagonist for nicotine acetylcholine receptors & thus may improve abstinence by blocking the rewarding effects of nicotine rather than by reversing withdrawal induced depression (Slemmer et al., 2000)

- supported by the observation that antidepressants with no affinity for nicotine acetylcholine receptors have no efficacy for smoking cessation (Hughes et al., 2007).

The efficacy of Bupropion as a smoking cessation agent has now been established in a multitude of randomised clinical trials & has a small superiority over NRT in promoting abstinence (Wu et al., 2006).

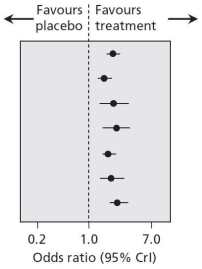
13

Varenicline (Champix) for smoking

Based upon the observation that both a nicotine agonist (NRT) & a nicotine antagonist (Bupropion) were effective in treating smoking cessation, Pfizer rationalized that a partial agonist would combine both properties & be more effective as a treatment than either alone

- acetylcholine partial agonist would serve as a weak nicotine replacement agent activating acetylcholine neurons to reverse withdrawal related hypofunction, but would also block the acute stimulating (rewarding) effects of smoking by competing with nicotine from smoking (Rollema et al., 2007)
- Varenicline has now been demonstrated to be more slightly more effective as a smoking cessation agent than either NRT or Bupropion (Wu et al. 2006; Eisenberg et al. 2008) although the absolute quit rates remain low: with short term abstinence being 25% for Varenicline vs 15% for placebo.

Pharmacotherapy	Odds ratio (95% CrI)
Bupropion	2.12 (1.76–2.56)
Nicotine gum	1.65 (1.37–2.01)
Nicotine inhaler	2.18 (1.38–3.45)
Nicotine nasal spray	2.37 (1.57–3.60)
Nicotine patch	1.88 (1.60–2.22)
Nicotine tablet	2.06 (1.47–2.87)
Varenicline	2.55 (1.99–3.24)



Eisenberg et al. (2008)

14

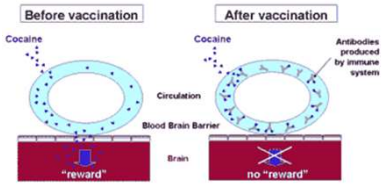
Treatments for stimulant addiction

Despite many years of testing, there is currently no effective medication for cocaine or amphetamine addiction (Leiderman et al. 2005; Kampman et al. 2005). Drugs that antagonise dopaminergic transmission were the first assessed because they should block drug reward.

- Acute administration of dopamine receptor antagonists reduced experience of cocaine reward in humans (Romach et al. 1999). Repeated administration of dopamine antagonists actually increased cocaine usage in human clinical trials (Haney et al. 2001) & animal models (Kleven & Woolverton 1990).

Upcoming medications are vaccines which set the immune system to breakdown cocaine & thus blunt its rewarding effects (Wee et al. 2012) & N-acetylcysteine which normalizes decreased glutamate levels in the nucleus accumbens following cocaine self-administration (Baker et al. 2002) & shown to reduce cocaine desire in humans (LaRowe et al. 2007).

However, none of these agents has been shown to be effective in promoting abstinence in randomised clinical trials. Research funding agencies, have placed a high priority on the establishment of a medication for psychostimulant addiction.



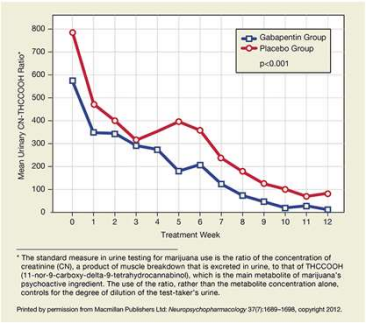
15

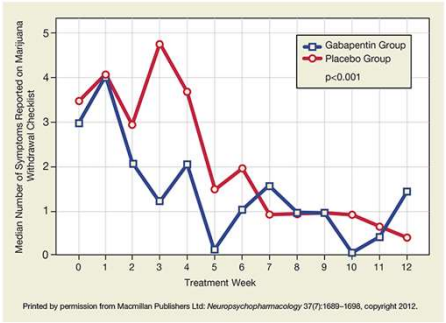
Treatments for cannabis addiction

Despite the demand for treatment there is currently no evidence based pharmacotherapy for cannabis dependence (Copeland & Swift 2009; Hart 2005). THC activates CB1 receptors to retroactively inhibit other cells, increasing overall brain inhibition. Following cannabis withdrawal, the brain shifts to a state of over-excitation.

Gabapentin: analogue of the inhibitory neurotransmitter GABA approved for the treatment of epilepsy Mason et al. (2012): 12-week, randomized, double-blind, placebo-controlled trial, 50 treatment-seeking outpatients with current cannabis dependence were given either Gabapentin or placebo.

- Gabapentin reduced both cannabis use & withdrawal symptoms over the 12 week period.
- It remains a question as to whether Gabapentin will improve long-term abstinence rates.





16

Cognitive enhancers

The ability to quit using drugs is impaired by a number of dysregulated traits, including cognitive impairment. Thus, it has been proposed that cognitive enhancing drugs may promoting abstinence.

- A large number of compounds satisfy the broad definition of a cognitive enhancer (i.e. they improve performance on some metric of behaviour or cognition).
- None of these cognitive enhancers has compelling evidence for efficacy in treating addiction. Nor have studies comprehensively tested whether the cognitive enhancing effect of the compound per se, is crucial for any pre-clinical therapeutic action observed.
- Thus, while the potential utility of cognitive enhancers has a compelling rationale, empirical evidence of an effective treatment remains a future prospect.

Name	Action
Donepezil, Galatamine, rivastigmine	Acetylcholine indirect agonist
Methylphenidate (Ritalin)	dopamine, noradrenaline & glutamate indirect agonist
Modafinil	Complex effects on almost all neurotransmitters
Atomoxetine	Noradrenaline & dopamine indirect agonist
Guanfacine	alpha-2 adrenergic receptor agonist
D-Cycloserine	Partial glutamate NMDA receptor agonist
Memantine	Non-competitive glutamate NMDA receptor antagonist
N-Acetylcysteine	Antioxidant & glutamate modulator

Brady (2011)

17

Summary

Knowledge & an understanding of:

- rationale, neuropharmacological mechanisms, effects and treatment efficacy of acamprosate, naltrexone & disulfiram in treating alcohol dependence.
- rationale & neuropharmacological mechanisms of methadone & suboxone.
- rationale & efficacy of Nicotine Replacement Therapy (NRT)
- rationale, neuropharmacological mechanisms & efficacy of bupropion & varenicline as pharmacotherapies for nicotine dependence.
- lack of pharmacotherapies for psychostimulant dependence & potential future directions.
- rationale behind the use of Gabapentin to treat cannabis dependence & it's treatment potential.
- cognitive enhancers & why they have been identified as potential pharmacotherapies for addiction but for the moment their efficacy is yet to be determined.

18