

## Repurposing of Old Treatments for New Indications: A Focus on Neuropsychiatric Disorders

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**Received:** May 02, 2018; **Published:** June 08, 2018

There are a plethora of biomedical treatments used in mainstream medical practice, some dating back for centuries. Despite the aging of most populations worldwide and the increasing global burdens of various diseases in recent decades, there has been a relative paucity in development of new treatments for neuropsychiatric conditions in particular. This is potentially due to big pharma retreating, micro-economic and macroeconomic constraints and the fastidious process of developing and then testing new molecules or treatments on a complex human brain. The benefits of psychological, behavioural, mutual help and standard medical treatments for a particular condition can be well known and accepted, however, limitations may include cost, logistics, treatment resistance and tolerability.

Amongst neuropsychiatric disorders alone, there are a number of potentially beneficial repositioned treatments for which little or no research or consensus exists. There can also be significant dissonance between scientific knowledge and delayed clinical practice.

Our history is replete with scientific achievements with respect to repurposing, such as sildenafil (cardiovascular disorders, repurposed and marketed for erectile dysfunction) and transcranial magnetic stimulation (originally for diagnostic purposes, now a routine treatment for major depressive disorder and potentially other neuropsychiatric indications). Phytocannabinoids have been used since antiquity in ancient Greece, Persia, China, Egypt, Netherlands and India for a variety of indications, with more recent evidence emerging for certain circumscribed conditions such as refractory epilepsy and chemotherapy-induced nausea. Some other examples of contemporary repurposing are shown in table 1.

The modern era of medicine comes with its hope but also a degree of constriction which conflates to drive flexible and creative ways of treating refractory neuropsychiatric conditions. Repurposing efforts should ideally be medically driven, ethically and legally approved, and objectively and subjectively monitored for a finite period of time. In the case of “off-label” or “un-approved” indication or route of administration, then the author recommends consideration and documentation of ethical principlism including fully informed consent, corporate counseling, second opinions and documentation of a risk-benefit matrix.

Drug/Compound	Original Indication	Accepted or Potential Repurposed Indication
Lamotrigine	Epilepsy	Bipolar affective disorder [1].
Topiramate	Epilepsy, migraines	Alcohol use disorder [2], PTSD [3], binge eating disorder and bulimia nervosa [4], ovarian cancer [5].
Tamoxifen	Breast cancer	Mania [1].
Botulinum toxin	Muscular spasticity	Major depressive disorder [6].
Pramipexole	Parkinson's disease	Major depressive disorder [7], bipolar affective disorder - depressive phase [8].
Ketamine	Anaesthesia	Major depressive disorder, post-traumatic stress disorder [9].
Flumazenil	Benzodiazepine reversal in bolus doses	Infusion IV or SC over days to weeks for treating benzodiazepine abstinence syndrome [10-12]. Now recognized as a neutral allosteric modulator.
Repetitive Transcranial Magnetic Stimulation	Major depressive disorder	Potentially for tinnitus [13], MDDS [14], cerebrovascular accidents [15,16].
Oxytocin	IV for uterine contraction during parturition.	Alcohol use disorder, autism, ADHD, social phobia, medication induced sexual dysfunction [17-28].
Isradipine	Hypertension	Parkinson's disease, stimulant (cocaine) use disorder [29].
Lisdexamfetamine	ADHD	Binge eating disorder, stimulant (methamphetamine) use disorder as replacement therapy [30].
Cannabinoids/ Phytocannabinoids	Used as anti-pyretic, anaesthetic, anti-inflammatory, analgesic and anti-emetic by many ancient civilisations.	Varies with nationality. In Australia, legal after application for indications of "chemotherapy-induced nausea and vomiting, epilepsy, multiple sclerosis, chronic non-cancer pain and palliative care" [31].
Naltrexone	Opioid antagonism	Alcohol and stimulant use disorders, gambling disorder, body focused repetitive behaviours [2,31-35]. Oral, injectable and implant formulations have now been developed.

**Table 1:** PTSD: Post Traumatic Stress Disorder; IV: Intravenous; SC: Subcutaneous; MDDS: Mal De Debarquement Syndrome; ADHD: Attention Deficit Hyperactivity Disorder.

The reasons driving a request (or behest), acceptance or reluctance to trial old approaches for novel reasons is often not congruent with evidence or based on biological plausibility. The scope for further research with many of these treatments is limited due to lack of financial incentives, but potentially less onerous if safety has been established in previous Phase I and II trials for other conditions.

**Disclosure of Interest Statement**

The author declares no conflict of interests related to this manuscript. TM has received honoraria, fees and/or provision of professional development resources from Servier, Otsuka/Lundbeck, Australian and New Zealand Mental Health Association, and Health Care. TM is currently the investigator for a site undertaking phase III research with flumazenil for which he is not remunerated and has no financial investment.

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**Volume 10 Issue 7 July 2018**

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