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Newer approaches to opioid detoxification

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Abstract

Opioid use disorders present with distressing withdrawal symptoms at the time of detoxification. The pharmacological agents and methods currently in use for detoxification mainly include buprenorphine, methadone, and clonidine. Many other pharmacological agents have been tried for opioid detoxification. This review takes a look at the newer pharmacological options, both opioid agonists and non-agonist medications that have been utilized for detoxification. Peer reviewed articles were identified using PubMed and PsychInfo databases. The keywords included for the search were a combination of 'opioid' and 'detoxification' and their synonyms. All the articles published in the last 10 years were screened for. Relevant data was extracted from identified studies. Many newer pharmacological agents have been tried in detoxification of opioids. However, the quest for a safe, efficacious, cost-effective pharmacological option which requires minimal monitoring still continues. The role of non-pharmacological measures and alternative medicine needs further evaluation.

Keywords: Alternatives, detoxification, modifications, newer techniques, opioid

Opioids have been in use by mankind for centuries. These act primarily on the opioid receptors in the body and carry a very high potential for dependence.[1,2] Their abuse has been world-wide; India is home to an estimated 2 million opioid dependent subjects.[3] Opioid abuse leads to health costs for the individual and socio-economic costs for the society;[4] while cessation of illicit opioid use is associated with improvement in physical health and social functioning.[5,6,7] Thus, opioid abuse is a big challenge for the entire humanity, and there is a social desire that abusers must come off this abuse. However, stopping of opioid use is associated with discomforting withdrawal symptoms: Muscle aches and pains, loose stools, piloerection, irritability, sleep disturbances, sympathetic activation, rhinorrhoea and lacrimation. Detoxification involves the process of withdrawing an individual from a specific psychoactive substance in a safe and effective manner, thereby minimizing the withdrawal symptom.[8]

Various methods used for opioids detoxification are: Abrupt cessation without using withdrawal syndrome ameliorating medication ("cold Turkey"), and cessation using either withdrawal syndrome ameliorating medications, and/or techniques from alternative medicines. The medications used, and gradually tapered off, are either opioid agonists or other non-agonist medications for symptomatic management. The opioid agonists used commonly for opioid detoxification include methadone, buprenorphine. The non-opioid medications used include alpha-2 adrenergic agents.[9] Additional medications often required and used concurrently, especially with non-opioid medications, include hypnotics and analgesics.

The detoxification can be carried out either on inpatient or outpatient basis. The detoxification can be ultra-rapid (under general anesthesia or heavy sedation), rapid (over 3-6 days), short-term (1-3 weeks) or long-term (over months). The present methods of detoxification pose some challenges and concerns. The side-effects of the medications, persistence of withdrawal symptoms, potential of diversion, and abuse, and need for monitoring are some of the problems encountered. These contribute to high rates of dropout and relapse. Hence, the search for an ideal pharmacological agent for detoxification continues.

An ideal agent for opioid detoxification should relieve withdrawal symptoms effectively, require minimal monitoring, and have negligible side effects and no abuse potential. In the last decade or so many medications and non-medication approaches have been tried for opioids detoxification. This review looks at these approaches.

SEARCH STRATEGY

The relevant peer reviewed articles were identified using PubMed and PsychInfo databases. The search was conducted in October 2011. The keywords included for the search were a combination of 'opioid' and 'detoxification' and their synonyms. All the articles published in the last 10 years were screened. A total of 659 abstracts were identified. The abstracts were further looked into for description of a newer or an alternate technique of detoxification. Those using buprenorphine, methadone or clonidine were excluded. For sake of summarizing, only a review article relating to lofexidine was included. The data regarding the methodology and results were further extracted from the identified studies, which are mentioned in this review.

Newer opioid agonist regimen of opioid detoxification

In the last decade or so various opioid agonists have been introduced for opioid detoxification in the newer formulations [Table 1]. These opioid

agonist act on the opioid receptors (primarily μ receptors, but also κ and δ receptors), and act as replacement for illicit opioids. They prevent significant withdrawals are tapered off over a course of days to weeks. The newer formulations use proven and effective detoxification agents, and intend to minimize the potential for diversion.

Buprenorphine, a partial μ-agonist and ê-antagonist has been widely used for detoxification. The newer formulations include a depot formulation, [10,11] as a transdermal patches[12] and in a high single oral dose.[13,14] The depot containing 58 mg of buprenorphine in microcapsules was injected subcutaneously. The transdermal patches come in varying strengths and release buprenorphine at a fixed rate. The patch used for detoxification released buprenorphine at 20 μg/h over a period of 7 days.[12] These formulations have been tried mainly in open label studies with small sample sizes. The results are encouraging and demonstrate efficacy of buprenorphine formulations in managing withdrawal symptoms.

Slow release oral morphine delivers a known quantity and purity of morphine, a natural opioid derived from opium poppy, in a controlled manner. It has been shown to be useful in opioid detoxification. A comparatively large double blind randomized controlled trial (RCT) has shown it to be efficacious.[15] It fared equivalent to methadone in attenuating withdrawal symptoms and reducing craving.

Dihydrocodeine, a semi-synthetic opioid analgesic used mainly as an anti-tussive, has also been utilized for opioid detoxification. It was found to be inferior to buprenorphine in reducing the withdrawal symptoms in two studies.[16,17]

Tramadol, is a synthetic opioid, which acts as a weak μ-opioid agonist, releases serotonin, and norepinephrine reuptake inhibitor. It has also been found to be less effective as compared to sub-cutaneous buprenorphine in a chart review study.[11]

Overall, in opioid detoxification the opioid agonists provide the advantages of effective control of withdrawal symptoms and reduction of craving. However, the potential of diversion and misuse remains with these agents.

Newer non-agonist regimen of opioid detoxification

Many non-opioids have been tried for opioid detoxification [Table 2]. Naltrexone, an opioid antagonist was used in a very low-dose as adjunct to methadone tapering in a community based blinded RCT. Its use was associated with attenuated withdrawal symptoms and craving.[18] Buspirone, is a serotonin 5-HT1A receptor partial agonist acting through the serotonin, dopamine, and noradrenergic systems. It was compared to methadone in a placebo controlled comparator RCT.[19] At doses of 30 mg and 45 mg/day, it was as effective as methadone in controlling the subjective and objective opiate withdrawal symptoms.

Venlafaxine, an antidepressant serotonin-norepinephrine reuptake inhibitor class, was used at doses of 300 mg/day in opioid dependent subjects in a placebo controlled RCT by Lin *et al*.[20] Compared to placebo the withdrawal symptom profile was similar, yet lesser amounts of ancillary medications were required with venlafaxine.

Quetiapine, an atypical antipsychotic acting through the dopaminergic and serotoninergic pathways, was tried for opioid detoxification in an open label study.[21] With 4 hourly use of 2 tablets 25 mg each there was reduced anxiety, pain and craving for the opioids.

Lofexidine, a newer α2 adrenergic drug, has been used in titrating the dose to a maximum of 1.6-3.2 mg/day in divided doses, given for 5-18 day-time.[22] It was shown to have lesser propensity to cause hypotension as compared to clonidine. However, withdrawal symptoms of insomnia and aching were not alleviated effectively.

Thus, the non-opioid methods offer advantage of lesser chances of misuse, as also better control of features of withdrawals like irritability. However, the overall reduction of withdrawal symptoms was not complete when compared with opioids.

Other measures

Apart from the pharmacological methods enumerated above, other non-pharmacological or alternative medical treatments have also been evaluated and shown to be beneficial in patients undergoing opioid detoxification. These methods that could possibly be used along with the regular pharmacological measures, have included Chinese herbal preparations,[23] qi-gong[24] and transcutaneous electric acupoint stimulation (TEAS).[25]

A meta-analysis of Chinese herbal preparations tried for opioid detoxification has been conducted.[23] Chinese herbal medicine was found to be superior to α2-adrenergic agonists in relieving withdrawal symptoms during 4^{th} to 10^{th} day, while both worked in an equivalent manner in the first 3 days. Compared with opioid agonists, Chinese herbal medicine was inferior during the first 3 days, but the difference was non-significant during 4^{th} to 9^{th} days. The herbal medicines were also reported to have lesser side-effects.

Qi-gong is a system of exercise that requires maintenance of certain postures for periods of time. Pan – gu qi-gong, a variety of qi-gong was tried in a RCT with medication and no-medication controls.[24] Reduction of withdrawal symptoms in the qigong group occurred more rapidly than in the other groups. As compared to medication group, the qi-gong group had significantly lesser anxiety, and less positive urine samples.

Meade *et al*.[25] tested the effectiveness of TEAS as an adjunctive treatment for in-patients receiving opioid detoxification with buprenorphine-naloxone. TEAS given in three 30-min treatments daily for 3-4 days was associated with better outcomes, greater improvements in pain and physical health.

It must be acknowledged that in patients being detoxified, a supportive environment, avoidance of cues that elicit craving and good nursing care would greatly reduce the distress and dropouts. The rapidity of taper should be individualized and gradual, as faster tapering is associated with use of substances.[26] Adjunct psychotherapy has been found to be linked to higher retention rates and lesser opioid use in patients undergoing detoxification.[27] The presence of other medical, psychiatric, and substance use comorbidities need to be addressed.[28]

CONCLUSION

The last decade has seen many new medications and techniques being used for opioid detoxification. None of these however, has been an ideal one. Hence the search for an agent or method which is safe and effective for opioid detoxification, has minimal abuse potential, requires minimal monitoring and is cost-effective still continues.

Footnotes

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Figures and Tables

Table 1

Authors	Study type	Intervention	Study subjects	Results
Sobel *et al.* (2004)[10]	Open label study	Single depot injection of 58 mg buprenorphine	5 opioid dependent volunteers	Depot showed effective relief from opioid withdrawal, showed to be safe and well-tolerated
Threlkeld *et al.* (2006)[11]	Chart review	Subcutaneous buprenorphine versus oral tramadol	115 opioids dependent subjects	Tramadol treated patients had significantly: Higher average withdrawal symptoms, greater reduction in withdrawal symptoms, similar side effect rates
Lanier *et al.* (2008)[12]	Open label study	Single 7-day application of transdermal patch of buprenorphine	12 opioid dependent subjects in an inpatient setting	Withdrawal was significantly reduced within 24 h, no significant withdrawal following patch removal
Assadi *et al.* (2004)[13]	RCT, double blind	Single dose of oral 12 mg buprenorphine in 24 h versus conventional doses of buprenorphine tapered over 5 days	40 opioid dependent inpatients	Time to maximal withdrawal symptoms was earlier in the single dose group. AST levels elevation lower in the single dose group. Single dose was well tolerated
Ang-Lee *et al.* (2006)[14]	Open label study	24 mg buprenorphine single oral dose	5 opioid dependent subjects	Could be used safely and effectively, use of ancillary medications was minimal, One episode of precipitated withdrawal resolving in 4 h
Madlung-Kratzer *et al.* (2009)[15]	RCT, double blind	Slow release oral morphine versus Methadone	208 opioid dependent patients maintained on methadone	Treatment groups similar for signs and symptoms of opiate withdrawal, craving for opiates, self-reported symptoms and physical symptoms, laboratory parameters
Wright *et al.* (2007)[16]	RCT, non-blinded	Dihydrocodeine versus buprenorphine	60 opioid dependent subjects in primary care setting	Buprenorphine had higher rates of completion and higher rates of abstinence
Sheard *et al.* (2009)[17]	RCT, non-blinded	Dihydrocodeine versus buprenorphine	90 opioid dependent prisoners	Buprenorphine had higher number of urine samples negative for opioids

RCT – Randomized controlled trial; AST – Aspartate transaminase; SROM – Slow release oral morphine

Alternative opioid agonist regimen/formulation for detoxification

Table 2

Authors	Study type	Intervention	Study subjects	Results
Mannelli *et al.* (2009)[18]	RCT, double blind	Low dose naltrexone (0.25 mg, 0.50 mg) adjunct to methadone tapering over 6 days	174 subjects attending community treatment programs	Attenuated withdrawal symptoms and craving
Buydens-Buydens-Branchey *et al.* (2005)[19]	RCT, double blind	Placebo Methadone taper Buspirone 30 mg Buspirone 45 mg	29 heroin dependent patients maintained on 30 mg methadone	Buspirone as effective as a methadone taper in alleviating the withdrawal symptoms, buspirone has less propensity of abuse than methadone
Lin *et al.* (2008)[20]	RCT, double blind	Venlafaxine (300 mg) versus placebo	34 heroin dependent inpatients	No difference in clinical global impression, patient's impression of treatment. Need for ancillary medications less with venlafaxine
Pinkofsky *et al.* (2005)[21]	Open label study	Quetiapine, 8 tabs of 25 mg given, instructed to take 2 tabs 4 h	107 opioid dependent outpatients	Quetiapine reportedly reduced craving for opioids, reduced anxiety, reduced somatic pain, alleviated insomnia and improved appetite

Alternative non-agonist regimen/formulation for detoxification