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Maintenance pharmacologic therapies for opioid use disorders: beyond opioid agonists

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Abstract: *Opioid use disorder is a worldwide challenge for an increasing number of patients, and still the therapeutic options presented in clinical guidelines for this condition are very few. The first line pharmacological therapies for opioid use disorder continue to be opioid agonists as substitution treatment, but the need to find new treatments without the effect of prolonging opioid dependence become more and more obvious. This systematic review presents the most supported by evidence pharmacological agents that can be used as monotherapy for opioid use disorder patients (i.e., naltrexone, extended release/implant and oral formulation), or as adjuvants to substitution therapy (e.g. olanzapine for aggressive behaviours, memantine or dextromethorphan for reducing inflammatory processes related to opioid use). More good quality data derived from larger, well designed trials are needed in order to find solid recommendations for non-opioid agonists in the treatment of opioid use disorder.*

Keywords*: opioid use disorder, naltrexone, memantine, dextromethorphan, olanzapine, maintenance treatment*

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INTRODUCTION

The importance of opioid dependence could not be overemphasized, and during the last decade a continuously increasing number of alerts have appeared both in public media and scientific environment regarding the negative functional impact, increasing societal costs and mortality risk associated with this pathology.

Opioid dependence is a significant contributor to the global disease burden, as between 24 and 35 million people globally used an illicite drug from this category in 2010 [1,2]. North America, Eastern Europe and Southern sub-Saharan Africa are the most strongly affected by the premature mortality related to opioid use disorder [1]. United Nations Office on Drugs and Crime 2017 Report shows an overall increase of the heroin and synthetic opioids use (oxycodone, hydrocodone, tramadol, and fentanyl) since 2009 and the trend to more diversification of the opioid market [3]. Disability-adjusted life years (DALY) attributable to opioid dependence in 2015 reached the value of 12 million, or 70% of the global burden of disease attributable to drug use disorder [4]. Relapse rate after detoxification is very high, ranging from 72% to 88% after 12-36 months [5].

Given consideration to the importance of opioid use disorder both at individual and societal level, worldwide efforts have been constantly made in order to find treatments able to prevent opioid use relapse and to maintain patients in remission as long as possible. The most validated treatments for the maintenance phase are methadone and buprenorphine, both with agonist actions at μ-opioid receptors (the first being a partial agonist, while the second is a full agonist). Unfortunately, due to their mechanism of action, both these drugs have abuse potential (less in case of buprenorphine) and associate withdrawal symptoms (although milder than in case of heroin or morphine). Therefore, the need to find non-addictive agents which can be used during the maintenance phase is considered urgent.

OBJECTIVE AND METHODS

This systematic literature review has as primary objective finding non-opioid agonist treatments for the maintenance phase in opioid use disorder patients, based on good quality data. The secondary objective is to formulate evidence-based recommendations for this indication, starting from existing data in the literature.

Table 1. Inclusion/exclusion criteria.

Operational criteria	Inclusion criteria	Exclusion criteria
Population	Minimum age for inclusion was 18 years, no superior age limit was established. The main diagnosis was opioid use disorder. Secondary diagnoses were allowed, if the study design permitted statistical analysis for at least one outcome regarding opioid use disorder. Diagnosis was established according to DSM-IV, IV TR, 5 or ICD-10 criteria.	Patients under age of 18. Presence of severe somatic or psychiatric co-morbidities that may have impact over patients' outcomes, or due to their treatment may lead to confusion about the outcome by pharmacokinetic or pharmacodynamic interactions.
Intervention	Any pharmacological agent without agonism (either partial or complete) over opioid receptors, either as add-on or as monotherapy. Combined pharmacological and psychological treatment. Treatment duration over 4 weeks.	Psychotherapy or psychological counselling as only type of intervention. Non-pharmacological and non-psychotherapeutical interventions, OTC, investigational products used in phase I, II or III clinical trials.
Environment	Inpatients, outpatients. Hospitals, day care, special care, intermediate care units. Carceral environment.	Unspecified environment.
Primary and secondary outcomes	Changes in opioid use- related parameters, e.g. days of abstinence, number of toxicology tests negative, rate of rehospitalisation for opioid consumption. At least one outcome is related to the opioid use.	All trials with outcomes not related to the severity of opioid use disorder.
Study design	Prospective or retrospective clinical trials. Randomized, open label, single blind, or double blind. Case control studies. Epidemiological studies. Observational trials.	Trials with unspecified or insufficiently specified design. Variables referring to opioid use disorder were not included in statistical analysis, or not presented in the published paper. Systematic review, narrative reviews, meta-analyses, case reports, case series.
Language	English, French, German, Russian	Any other language, except for those already specified.

Methods were based on the qualitative review of data found in the main electronic databases- PubMed, Complete MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Library of Medicine and the National Institute of Health (NCBI), PsychInfo and Thomson Reuters/Web of Science. All clinical trials and epidemiological studies published between 1998 and 2018 in English, French, German, and Russian were included in the primary review. The search paradigm used was „opioid dependence", „opiate dependence", „opioid/opiate use disorder", combined with „non-opioid agonists" or „non-opioid pharmacological treatment". This literature review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) principles of research [6].

Inclusion and exclusion criteria were applied to all papers found during primary search (table 1).

Therapeutic intervention was focused on drugs with non-opioid agonistic properties. If any psycho-therapeutic intervention was administered, than it was only as an add-on to the pharmacologic management, and not the main method of treatment. Because this review was focused on maintenance therapy, brief interventions were not included. The outcomes of therapeutic intervention had to be periodically evaluated, and statistically analysed. Only trial which produced inferential, statistically-based data were included in the final step of the review.

During the secondary analysis, papers were reviewed and their results were analyzed. Only papers to which full text was found were included in the final analysis.

All studies were ranked according to their level of significance (LOS). This level was determined based on the quality of the study design: (5) double-blind randomized controlled trial, with/without an active comparator/placebo; (4) single-blind trials, with/ without an active comparator/placebo; (3) open-label trials with/without an active comparator; (2) retrospective studies, observational trials; (1) any other study design.

GRADE recommendations for the level of evidence [7] were formulated based on the evidence found in the secondary analysis. GRADE recommendations included 5 levels: A= high quality= future research are very unlikely to change the validity of these recommendations; B= moderate quality= future research is likely to have an important impact on the appreciation of the recommendations; C=low quality= it is very likely that future research will have an important impact over the confidence in the estimate of effect and is likely to change the recommendations; D= very low quality= any estimate of the effect is very uncertain. Intermediate steps (+ or -) represent nuances of the recommendations based on the quality of trials and tolerability of intervention, as resulted from these trials [7].

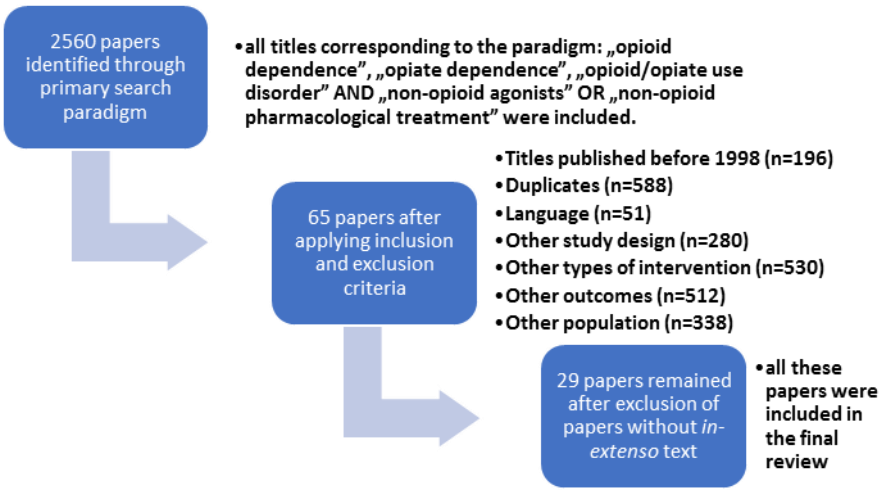
RESULTS

After the primary search 2560 papers surfaced, but only 65 remained when the inclusion and exclusion criteria were applied (figure 1). A number of papers were excluded because full text was not found, so that 29 studies remained to be reviewed in the final step. All trials included in the secondary review are presented in table 2.

These 29 trials included in the secondary analysis had a total number number of participants of 3,159, and a mean LOS of 3.58. A number of 13 trials were found to be high quality designed trials (LOS=5), meaning double-blind, either placebo-controlled or with an active comparator, randomized clinical trials.

Analysis of interventions corresponding to the inclusion/exclusion criteria previously mentioned showed that non-opioid agonist drugs used in the maintenance phase in patients with opioid use disorder who have been previously detoxified were: (1) naltrexone implant; (2) oral naltrexone; (3) topiramate; (4) memantine; (5) dextromethorphan; (6) dronabinol; (7) olanzapine; (8) baclofen; (9) ibudilast; (10) buspirone; (11) sodium valproate; (12) fluoxetine; (13) paroxetine; (14) clonazepam; (15) gabapentin. The last five drugs were used only in combination with another active medication or as active comparators, so they were not evaluated separately in this review.

Figure 1: Stepwise filtration of titles found during electronic databases search



Naltrexone was the most investigated non-opioid agonist medication for the maintenance therapy in opioid use disorder, and 15 relevant trials focus on this drug's efficacy have been found during the secondary search. Naltrexone is an opioid antagonist, and both the parent drug and its active metabolite (6β-naltrexol) are competitive antagonists of the μ-, and to a lesser extend to κ- and δ-opioid receptor (10-25 times lower affinity for κ- and δ-receptors compared to the μ-receptors) [8]. Because oral naltrexone is extensively metabolized during first-pass metabolism, and because therapeutic adherence of opioid users is known to be very low, various implant formulations of this pharmacological agent have been developed.

Oral formulation of naltrexone has been investigated in comparison with buprenorphine/naloxone in the post-detox phase [9], methadone in stabilized patients [10], buprenorphine and placebo in detoxified patients [11], methadone in opioid dependent patients who were stablized on methadone maintenance treatment for controlling depressive and anxiety symptoms [12]. Oral naltrexone as monotherapy was compared with naltrexone plus gabapentin (1200 mg/day) for the management of muscle pain and craving [13], and naltrexone plus placebo was compared with naltrexone plus sertraline for controlling depression severity and opioid craving [14]. Another trial compared naltrexone (50 mg/day) + fluoxetine (20 mg/day) with naltrexone + placebo, fluoxetine + placebo, or placebo for 6 months plus psychotherapy for all groups for the monitoring of remission rate during 6 months [15]. The mean LOS of these studies was 3.85, and an overall number of 657 patients were included.

These trials supported a moderate efficacy and tolerability of oral naltrexone: buprenorphine/naloxone was superior to naloxone in the reduction of opioid-positive urine test and preserving patients participation in the treatment [6], naltrexone induced similar weight gain during 6 months of treatment when compared to methadone [16], naltrexone may improve depression in patients with opioid use disorder at 6 months [12], and naltrexone was inferior to buprenorphine (not statistically significant) in several outcomes regarding the rate of relapse in detoxified heroin dependent patients [11].

Naltrexone plus fluoxetine and individual psychotherapy has been proven a useful combination especially in women with heroin dependence, because it increased the remission rate and maintenance of remission in this population [15]. Naltrexone plus gabapentin improved muscle pain and psychological dependence severity in patients dependent on pentazocine [13]. Naltrexone plus sertraline was a well-tolerated combination and increased on short-term treatment retention of recently non-depressed opioid abstinent patients, but the difference between this combo and naltrexone alone disappeared in time [14].

Naltrexone extended-release has been investigated in comparison with buprenorphine/naloxone [16], treatment as usual [5], oral naltrexone plus psychosocial therapy [17], and methadone [18]. Naltrexone implant was investigated also in several trials as single pharmacological agent, without an active comparator [19-22]. The mean LOS of these trials was 2.8, and the global number of participants was 1982.

The overall efficacy of naltrexone extended-release was good, although data are derived from poor and medium-quality designed trials. Its efficacy and tolerability were similar to buprenorphine/naltrexone in patients who wanted to switch from this combination of drugs to naltrexone implant [16], and it induced a lower rate of relapse when compared to treatment as usual, at least on short-term [23]. Heroin dependent patients who received extended release formulation of naltrexone had better outcomes than those treated with oral formulation of the same drug [17], and naltrexone implants but not methadone were associated with long-term benefits in decreasing opioid-related hospital morbidity [18].

In trials without an active comparator, naltrexone extended-release was efficient in preventing opioid overdose [22], improved depression severity at 4 weeks post-baseline, but it may also be responsible of worsening late insomnia [21], improved quality of life, rate of retention, opioid-negative urines, opioid craving, and rate of re-employment [20]. Also, naltrexone plus psychological counselling improved the acceptance of opioid dependence pharmacotherapy and prolonged the duration of abstinence to opioids, when compared to placebo plus counselling [19].

Topiramate is an anticonvulsant with GABA-enhancing properties and AMPA and kainate-inhibitory actions, involved in the modulation of extracellular dopamine release in the mesocortical and limbic system dopaminergic system, properties which recommended it as a potential treatment for cocaine dependence [24]. Patients with opioid use disorder who presented also cocaine dependence did not benefit from the addition of topiramate to their methadone maintenance therapy, because no difference to placebo could be found after 12 weeks [25].

Ibudilast is an anti-inflammatory drug with phosphodiesterase inhibition properties (especially PDE4) which has been associated in animal studies with the capacity of alterating several opioid-mediated effects [26, 27]. When compared with placebo in a 6-week RCT in patients detoxified from morphine, ibudilast treated patients presented lower rates of drug liking (oxycodone), lower craving to heroin/ tobacco/cocaine and lower subjective ratings of pain vs. placebo [26].

Memantine is a noncompetitive NMDA-receptor antagonist that blocks the effects of excessive concentrations of glutamate, currently used for Alzheimer Disease- related neurocognitive disorder and researched intensively for other dementias, ADHD, and as an agent able to reverse tolerance to opioids [28]. Memantine was administered in patients who were on buprenorphine/naloxone maintenance treatment, and compared to placebo [29], or in patients who were on methadone-maintenance-therapy, compared to placebo plus methadone-maintenance therapy [30, 31]. Memantine was also investigated as maintenance treatment in detoxified non-treatment seeker heroin dependent patients during 8 weeks of in-patient regimen [32].

These trials investigating the efficacy of mematine had a mean LOS of 4.25, and an overall number of 350 participants. It can be observed that the quality of trials focused on memantine efficacy was higher than previously mentioned research for other investigational products.

Memantine has been proven as a useful adjunctive medication for patients treated with buprenorphine/naloxone and it may provide an easier transition to buprenorphine-free therapeutic regimen [29]. Low dose memantine attenuated chronic opioid-dependence-induced cognitive impairment, decreased the daily dose of methadone, and had positive effect over probably NMDA-mediated inflammatory processes [30, 31]. Memantine decreased the subjective, but not the reinforcing

effects of heroin in non-treatment seeker heroin-dependent patients [32].

Dronabinol is a synthetic form of 9-tetrahydro-cannabinol, with similar affinity for cannabinoid 1 and 2 receptors, currently approved for use in anorexia associated with weight loss in AIDS and for the treatment of nausea associated with chemotherapy resistant to other anti-nausea treatments [33]. A double-blind, placebo-controlled RCT investigated the effects of dronabinol in patients with naltrexone extended release and a significant effect of this drug in decreasing the severity of opiate withdrawal has been proven [34].

Dextromethorphan is an antitussive drug with N-methyl-D-aspartate (NMDA) receptor antagonist properties, involved also in protecting monoaminergic neurons against inflammation-mediated degeneration [35, 36]. Chronic opioid administration produces systemic inflammation, and for this reason the use of a drug with anti-inflammatory properties seems to be granted [37]. Based on its neuroprotective and anti-inflammatory properties, dextromethorphan was investigated as adjunctive agent in patients with opioid use disorder. Dextromethorphan 60 mg/day and 120 mg/day were compared with placebo as adjunctive to methadone treatment in opioid-dependent patients [37, 38], and in another trial dextromethorphan 240 mg/day was compared with placebo in methadone-stabilized patients [39].

These trials with dextromethorphan had a mean LOS of 5, and a total of 268 patients.

Dextromethorphan was useful in low doses as adjuvant treatment in methadone-treated patients both at inflammatory level and clinical level [37, 38], but in another trial the difference versus placebo was not significant in the otcome defined as mean methadone consumption [39]. The quality of life was superior in patients who reeived dextromethorphan as adjuvant to methadone versus placebo plus methadone [39].

Olanzapine is an atypical antipsychotic investigated in patients with opioid dependence who were on substitution therapy, as a drug targeting the aggresive behavior [40, 41]. The mean LOS of these trials was 3.5, and the total number of participants was 268.

In the first trial, olanzapine (2.5-15 mg) was compared with sodium valproate (600-1000 mg) in patients stabilized on methadone, and olanzapine was slightly superior in controlling aggressivity but did not differed from valproate in reducing the number of positive urine samples [40]. In the second, smaller-sample size, olanzapine was compared to fluoxetine/paroxetine and clonazepam and reduced aggressive/hostile behavior in heroin addicted patients undergoing substitution therapy [41]. In this second trial, olanzapine was superior to its comparators in the direct aggressiveness, overall hostility, verbal aggressiveness, and aggressive incidents; also, 70% of the completers achieved full remission, without significant differences between groups [41].

Buspirone is a non-benzodiazepine anxiolytic which possesses 5HT1A agonistic properties, acting as full agonist at 5HT1A presynaptic receptors and partial agonist at postsynaptic 5HT1A receptors [42]. A single trial that compared buspirone with placebo in patients with anxiety undergoing methadone therapy has been identified during the literature review [43]. Buspirone had no significant efficacy over anxiety symptoms in these patients, but it decreased depression severity and slowed down the return to substance abuse [43].

Baclofen is a GABA-B receptor agonist that may be helpful in promoting abstinence from a variety of drugs [44]. A double-blind, placebo-controlled, 12-week RCT with a LOS of 3, which included 40 patients with opioid dependence, recently detoxified, found a significantly better treatment retention in the baclofen-treated patients (60 mg/day) [45]. This trial had a small sample size and a high attrition rate, which make difficult to generalize its results.

Table 2. Trials focused on non-opioid agonist therapies during the post-detoxification phase in patients with opioid use disorder

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Pirnia B, Soleimani AA, Malekanmehr P, et al. [25]	Placebo-controlled RCT; topiramate (25-300 mg/day), 12 weeks, escalating doses; patients were treated also with methadone 20-140 mg/day and brief behavioral compliance enhancement treatment for cocaine dependence.	n=50 patients with dual cocaine and opiates dependence	Weekly urine drug screens.	Topiramate was no better than placebo in reducing cocaine use, but was superior to placebo in reducing cocaine craving.	The efficacy of topiramate in cocaine use reduction in patients with dual cocaine and opiates dependence was not supported.	5
Solli KK, Latif ZE, Opheim A, et al. [16]	Prospective cohort study, naltrexone-extended release vs. buprenorphine-naloxone 3 month + participants' choice of study medication for an additional 9 months; the active drug was administered every 4 weeks (380 mg).	n=54 opioid-dependent adults continuing naltrexone-extended release and n=63 opioid dependents inducted on the same treatment	Use of heroin and other illicit substances, opioid craving, treatment satisfaction, treatment retention, adverse events, addiction-related problems	Follow-up after 9 months showed completion rates of 51.9% among participants continuing naltrexone-extended release in the follow-up and 47.6% among those inducted on the active treatment, with opioid abstinence rates of 53.7 and 44.4%, respectively.	Opioid-dependent individuals who elect to switch from buprenorphine-naltrexone after 3 months to extended release naltrexone 9 months were experiencing similar results (treatment completion and abstinence rates) and similar rate of adverse events to those who had been on extended-release naltrexone from the start.	4
Metz VE, Jones JD, Manubay J, et al. [26]	6-week RCT focused on ibudilast (a nonselective phosphodiesterase inhibitor) effects over craving, reinforcing, analgesic effects of oxycodone in human volunteers diagnosed with opioid dependence; patients received maintenance treatment with ibudilast (50 mg bid) or placebo	n=11 patients detoxified from morphine addiction	VAS for measurement of subjective effects of oxycodone.	Patients receiving active ibudilast presented decreased rates of drug liking after 15 mg of oxycodone; heroin/ tobacco/cocaine craving was reduced under active ibudilast vs. placebo; mean subjective ratings of pain were lower in the active ibudilast condition.	Ibudilast may be useful in treating opioid use disorder and may enhance the analgesic effects of oxycodone.	3

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Earley PH, Zummo J, Memisoglu A, et al. [20]	Single-arm, multisite, open-label study; extended release naltrexone injections for up to 24 months, combined with counselling via intensive outpatient substance abuse treatment programs.	n=38 enrolled opioid-dependent healthcare professionals who had been detoxified for at least 2 weeks	Opioid drug tests monthly, measurements for quality of life, opioid craving, and treatment satisfaction	At 24 months, mean opioid craving fell by 45.2% and quality of life (SF-36) -mental component score improved by 31.1% from baseline; of the 22 unemployed subjects at baseline, 45.5% improved employment status at 24 months.	Long-term extended release naltrexone was associated with better quality of life, rates of retention, opioid-negative urines, opioid-craving reduction, re-employment	3
Lee JD, Friedmann PD, Kinlock TW, et al. [23]	Open-label RCT, 24-week extended-release naltrexone vs. usual treatment (brief counseling and referrals for community treatment programs);	n=308 criminal justice offenders with history of opioid dependence, abstinent from opioids at the time of randomization	Time to an opioid-relapse event (defined as 10 or more days of opioid use in a 28-day period).	Participants assigned to extended-release naltrexone had a longer time to relapse than did those who received usual treatment, lower rate of relapse, and higher rate of opioid-negative urine samples. After one year, the rates of opioid-negative urine samples were equal. During one year, there were no overdose events in the extended-release naltrexone treated participants, while in the usual-treatment group there were 7 cases.	Extended-release naltrexone was associated with a rate of opioid relapse lower than that with usual treatment, but after one year the protective effects waned.	3
Mokri A, Chwarski MC, Taherinakhost H, Schottenfeld RS [9]	Single-site, two-parallel groups, double-blind RCT, 12-week; oral naltrexone vs. buprenorphine/ naloxone.	n=102 participants with opioid use disorder in the post-detox phase	Initial duration of opioid abstinence (urine toxicology tests).	Mean number of days of initial duration of verified abstinence was higher with buprenor-phine/naloxone (p=0.205); mean num-ber of opioid-negative urine tests was higher in the buprenorphine/ naloxone-treated subjects (p=0.049); the mean number in treat-ment was also greater in buprenorphine/naloxon e group (p=0.013); the rate of sustained, 12-week opioid abstinence was double in the buprenorphine/ naloxone group.	Sublingual buprenorphine/ naloxone was associated with a greater number of opioid-negative urine tests and treatment retention, but not significantly greater initial abstinence duration or proportions with sustained abstinence.	5

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Gonzalez G, DiGirolamo G, Romero-Gonzalez M, et al. [29]	Double-blind placebo-controlled RCT, 13 weeks; patients already received treatment with buprenorphine/naloxone 16/4 mg/day and they were randomized to memantine 15 mg or 30 mg vs. placebo.	n=80 young adults with opioid dependence	Change in the weekly mean proportion of opioid use, and cumulative abstinence rates after rapid buprenorphine discontinuation at week 9	Memantine 30 mg/day significantly improved short-term treatment with buprenorphine/ naloxone by reducing relapse and opioid use after buprenorphine discontinuation, during the last 2 weeks of study participation.	Memantine could be an useful adjunctive treatment at 30 mg daily for patients treated with buprenorphine/ naloxone and helpful in the transition to buprenorphine-free therapeutic regimen.	5
Bisaga A, Sullivan MA, Glass A, et al. [34]	Double-blind RCT, dronabinol 30 mg/day (n=40) vs. placebo (n=20); patient underwent inpatient detoxification for opioid dependence and extended-release naltrexone induction; dronabinol was administered while inpatient and 5 weeks afterwards.	n=60 patients recently de-toxified from opioids	Severity of opioid withdrawal and retention in treatment.	The severity of opioid withdrawal during inpatient phase was lower in the dronabinol group vs. placebo; rates of successful induction onto extended release naltrexone and completion of treatment were not significantly superior for dronabinol vs. placebo.	Dronabinol reduced the severity of opiate witdrawal but had no effect on rates of extended-release naltrexone treatment induction and retention.	5
Chang YH, Chen SL, Lee SY, et al. [30]	RCT, memantine plus methadone-maintenance-therapy (n_1=57) vs. placebo plus methadone-maintenance therapy (n_2=77); healthy controls were matched with methadone-treated group; 12 weeks duration of monitoring.	n=134 patients stabilized on methadone	Cognitive performances	Both treatment groups showed improvements in their cognitive performances. Memantine add-on was superior to placebo in the post-treatment cognitive improvement.	Low-dose memantine (5 mg/day) may attenuate chronic opioid-dependence-induced cognitive decline.	5
Lee SY, Chen SL, Chang YH, et al. [37,38]	12-week RCT, dextrometorphan 60 mg/day (n_1=65), 120 mg/day (n_2=65) vs. placebo (n_3=66) as adjunctive to methadone treatment in opioid-dependent patients.	n=196 opioid dependents	Methadone dose required, plasma morphine level, retention in treatment.	Patients who received 60 mg/day dextromethorphan had significantly longer treatment retention and lower plasma morphine levels than did the placebo group. Plasma TNF-alpha was significantly decreased in the 60 mg dextromethorphan group compared to placebo.	Low dose dextromethorphan is useful as concomitant therapy in methadone-treated patients both at the pathogenic-inflammatory level, and at the clinical level.	5

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Lee SY, Chen SL, Chang YH, et al. [31]	Double-blind RCT, placebo-controlled, 12-week duration; memantine (5 mg/day) (n_1=53) vs. placebo (n_2=75); patients with opioid dependence undergoing methadone maintenance therapy.	n=128 patients stabilized on methadone	Inflammatory bio-markers, overall dose of methadone	Memantine-treated patients required a somewhat lower methadone dose than did placebo-group (p=0.039), and they also had significantly lower plasma TNF-α and higher TGF-β1 levels.	Low-dose me-mantine may help patients during metha-done substitu-tion treatment because of the overall methadone dose decrease and positive impact over inflammatory process possible related to the NMDA-receptors.	5
Krupitsky E, Nunes EV, Ling W, et al. [19]	Double-blind, placebo-controlled multicentric RCT, 24 weeks; 380 mg extended-release naltrexone vs. placebo; counselling sessions were provided for both groups.	n=250 patients with opioid dependence, who underwent detoxification	Confirmed abstinence (urine drug tests and self-report).	Extended-release naltrexone-treated patients had significantly longer periods of confirmed abstinence (p=0.0002), more opioid-free days (p=0.0004), less craving (p<0.0001), more treatment-retention (p=0.0042).	Extended-release naltrexone in conjunction with psychosocial treatment improve the acceptance of opioid dependence pharmacothera py and prolongs the duration of abstinence to opioids.	5
Krupitskii EM, Zvartau EE, Tsoi-Podosenin MV, et al. [15]	RCT, patients were randomized on naltrexone (50 mg/day) + fluoxetine (20 mg/day), naltrexone + placebo, fluoxetine + placebo, or placebo for 6 months; individual psychotherapy for the maintenance of remission was applied for all gropus (one session).	n=280 patients with heroin addiction	Remission rate, maintenance of remission	Naltrexone + fluoxetine was more effective than fluoxetine + placebo (p<0.01) and placebo (p<0.001) in the remi-ssion percentage. Naltrexone was superior to placebo and fluoxe-tine in the efficacy of maintenance of remi-ssion and preventing relapse in patients with heroin addiction. The combination of naltrexone and fluoxetine was more effective compared to naltrexone monotherapy only in women.	Naltrexone and fluoxetine could be useful in patients with heroin dependence, especially in women.	5

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Zarghami M, Sheikhmoonesi F, Ala S, et al. [40]	12-week RCT, olanzapine (2.5-15 mg) vs. sodium valproate (600-1000 mg).	n=201 patients on methadone maintenance treatment	Aggressive behavior, urine toxicology.	Olanzapine and sodium valproate reduced the overt aggression and subscales of irritability, aggression, and suicidality. Olanzapine-treated patients presented more improvement in aggressivity. The percentage of positive urine samples (morphine, cannabis, methamphetamine) were not significantly different between the study groups.	Olanzapine and sodium valproate may be useful as adjunctive agent in decreasing aggressive behavior in heroin dependent individuals during methadone substitution treatment, with a slightly superior effect of olanzapine.	4
Salehi M, Zargar A, Ramezani MA [39]	Double-blind RCT, dextromethorphan vs. placebo; 6-month follow-up.	n=72 opiate abusers with methadone maintenance therapy	Methadone consumption dosage, quality of life, withdrawal symptoms.	The mean methadone consumption in the dextromethorphan-treated patients vs. control group were 62.7 mg/day vs. 70.4 mg/day. Total mean score of the quality of life was superior in the intervention group ($p>0.05$).	Dextromethorphan might be useful for opioid dependence treatment, but the differences vs. placebo were not significant.	5
Brooks AC, Comer SD, Sullivan MA, et al. [17]	Quasy-experimental comparison, long-acting injectable naltrexone ($n_1=42$) vs. oral naltrexone ($n_2=69$). Psychosocial therapy was also initiated for these patients.	n=101 patients on naltrexone	Days retained in treatment, severity of drug use	Long-acting injectable naltrexone had been associated with better outcome than oral naltrexone on days retained in treatment and other measurements for opiate use, while still other measurements for opiate use were not significantly different; heroin users with more severe baseline use showed better retention with oral naltrexone maintenance therapy, while less severe heroin users evidenced better outcomes when treated with long-acting injectable naltrexone.	Superior outcomes for heroin-dependents who received long-acting injectable naltrexone compared to oral naltrexone.	2

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Mysels DJ, Cheng WY, Nunes EV, Sullivan MA [21]	Prospective evaluation using Hamilton Depression Rating Scale in patients treated with naltrexone depot maintenance and relapse prevention therapy; 2 and 4 -week post-baseline evaluations.	n=34 patients on naltrexone	Depression severity	Significant improvement of depression scores after 4 weeks post-baseline ($p<0.0004$), somatic and cognitive-affective subscales scores significantly decline; late insomnia increased significantly at 2 weeks post-baseline.	Naltrexone induction and maintenance does not worsen depression, but it may cause sleep impairments	2
Myesels DJ, Vosburg SK, Benga I, et al. [10]	Retrospective chart review; patients were maintained on methadone (n=16) or naltrexone (n=20);	n=36 opiate dependent patients stabilized on pharmacologic al treatment	Change in body weight from baseline to 3 months and 6 months into treatment.	No difference in weight was detected at baseline, 3 or 6 months between the two treatment groups.	No statistically difference over the weight between methadone and naltrexone maintenance treatment.	2
Schottenfeld RS, Chawarski MC, Mazlan M [11]	Double-blind RCT, 24 weeks; oral naltrexone vs. buprenorphine vs. placebo	n=126 detoxified heroin-dependent patients	Days to first heroin use (urine drug tests), days to heroin relapse, maximum consecutive days of heroin abstinence, reductions in HIV risk behaviours over 6 months.	Days to first heroin use, days to heroin relapse (3 consecutive positive tests), and maximum consecutive days abstinent had all supported the superiority of buprenorphine (significant to placebo). Differences between buprenorphine and naltrexone were not significant for days to heroin relapse and maximum consecutive days abstinent. Differences between naltrexone and placebo were not significant for any outcomes. HIV risk behaviours were significantly reduced by all three treatments.	Buprenorphine was superior to naltrexone, although for the most variables monitored the differences were not statistically significant.	5
Ngo HT, Tait RJ, Hulse GK [18]	Retrospective longitudinal follow-up; methadone (n_1=522) or naltrexone implant (n_2=314) as maintenance treatment for opioid- dependent patients. Evaluations at 6 months and 3.5 years post-treatment.	n=836 patients treated for opioid dependence	Hospital admissions rates, adjusted changes in risks and rates of overdose-related and non-overdose-related hospital morbidity associated with opioid vs. nonopioid drugs.	Naltrexone implant decreased risk for overdose and non-overdose-related events at 3.5 years, but not methadone; 5 drug-related deaths after methadone and 1 after naltrexone implantation.	Naltrexone implants, but not methadone, has been associated with long-term benefits in decreasing opioid-related hospital morbidity.	2

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Gerra G, Di Petta G, D'Amore A, et al. [41]	12-week prospective, observational trial; open-label study; olanzapine vs. fluoxetine/ paroxetine+ clonazepam for controlling aggressiveness.	n=67 patients with heroin dependence undergoing substitution therapy	Hostility scores, incidence rates of aggressive incidents and attacks.	Direct aggressiveness, overall hostility scores, verbal aggressiveness scores, aggressive incidents rates were significantly lower compared to baseline in patients treated with olanzapine who comple-ted the treatment. Among completers, almost 70% achieved full substance abuse remission, 30% partial substance abuse remi-ssion, without signifycant differences between groups.	Olanzapine may be useful as adjunctive treatment in reducing aggressive/hostile behavior in heroin addicted patients who undergo maintenance substitution therapy.	3
Dean AJ, Saunders JB, Jones RT, et al. [12]	Open-label RCT, naltrexone 50 mg/day (n_1=42) vs. methadone (n_2=38) in opioid dependent patients who were stablized on methadone maintenance treatment; 6-month duration.	n=80 patients stabilized on methadone	Depressive symptoms severity, anxiety symptoms severity.	Patients who received naltrexone did not exhibit worsening of depressive symptoms; in patients attending follow-up assessments, those who received naltrexone presented an improvement in depression over time, compared to the control group; adherence to naltrexone correlated with lower depression severity scores.	Naltrexone has a positive impact over depressive symptoms during maintenance treatment in opioid dependent patients.	3
Hulse GK, Tait RJ, Comer SD, et al. [22]	Cohort study, pre-post design, data were prospectively collected; patients were evaluated before and after treatment with a sustained release naltrexone implant; a subgroup (n=146) had previously received treatment with oral naltrexone.	n=361 heroin dependent persons	Primary outcome was overdose events.	21 overdoses involving 20 persons in the 6 months pre-treatment; none was observed in the 6 months post-treatment; blood naltrexone levels at or above 3 ng/ml for approximately 6 months after injecttion; reduced number of opioid overdoses were also observed 7-12 months after implant; for those previously treated with oral naltrexone, more opioid overdoses occured in both 6-month prior to and after oral compared to the 6-month post-implant treatment.	Sustained-release naltrexone implant is efficient in preventing opioid overdose.	2

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Comer SD, Sullivan MA [32]	Detoxified, non-treatment-seeker-heroin dependent patients; 8 weeks; 0, 30, 60 mg/day memantine as maintenance treatment; intranasal heroin (0, 12.5, 50 mg); inpatient regimen.	n=8 patients with heroin dependence	Subjective ratings of drug quality, liking, willingness to pay for drugs, craving.	Memantine produced modest reductions in subjective ratings of drug quality, liking, willingness to pay for the drug, and craving for heroin. It had little influence over the reinforcing heroin effects.	Memantine could be a useful agent for decreasing the subjective but not the reinforcing effects of heroin.	2
McRae AL, Sonne SC, Brady KT, et al. [43]	RCT, 12-week, placebo-controlled study; patients on methadone who presented also anxiety symptoms; buspirone vs. placebo.	n=36 patients receiving methadone maintenance treatment	Anxiety symptoms	Buspirone did not significantly decrease anxiety symptoms in opioid-dependent patients.	Buspirone had no significant efficacy over anxiety symptoms in subjects undergoing methadone maintenance treatment, but it was associated with reduction in depression scale scores and slower return to substance use.	5
Assadi SM, Radgoodarzi R, Ahmadi-Abhari SA [45]	Double-blind, placebo-controlled, 12-week RCT; patients received fixed-schedule baclofen 60 mg/day or placebo.	n=40 patients with opioid dependence, recently detoxified	The primary outcome was retention in treatment.	Treatment retention was significantly higher in the baclofen group (p=0.01); 30% of patients treated with baclofen completed the trial vs. 10% patients on placebo. The rates of opioid-positive urine samples did not differ significantly between the two groups. Baclofen was superior to placebo in terms of opiate withdrawal syndrome and depressive symptoms. Intensity of opioid craving and self-reported opioid and alcohol use were more favourably influnced by baclofen, although not statistically significant. The drug side effects of the two groups were not significantly different.	Baclofen could be useful in the maintenance treatment of opioid dependence, but the sample size was small, and the attrition rates were high.	5

Authors	Study design, description of therapeutic intervention	Patients	Primary outcomes	Results	Conclusion	LOS
Kumar P, Jain MK [13]	Open label trial; patients received clonidine (for detox) and later naltrexone p.o. (50 mg BD) as maintenance therapy vs. naltrexone plus gabapentin (1200 mg/day) for 3 weeks.	n=20 opioid dependent patients (pentazocine)	Muscle pain and craving (rated on visual-analogue scale), psychological dependence severity.	Patients receiving naltrexone + gabapentin scored significantly lower on both parameters- pain score and craving score ($p<0.001$), and psychological dependence was significantly lower in this group ($p<0.01$).	Gabapentin is efficient in controlling muscle aching, and no tolerance effect was observed after 3 weeks. Gabapentin may reduce pain in opioid dependent patients when added to naltrexone, signaling a possible synergistic effect. Gabapentin may help in controlling the opiate craving and potentiated the effect of naltrexone in this regard.	3
Farren CK, O'Malley S [14]	Double-blind, placebo-controlled trial, naltrexone 50 mg qd plus placebo vs. naltrexone 50 mg plus sertraline 50 mg qd; 12-week monitoring duration.	n=13 recently non-depressed abstinent opiate addicts	Depression severity, opiate craving, adverse events	Similar side effect profile in both groups, and similar retention rates. Significant negative correlation between Beck Depression Inventory scores and duration in treatment in the combined therapy group. Opiate craving decreased over time in both groups.	Naltrexone plus sertraline was well tolerated and initially successful in increasing treatment retention, but the difference to the naltrexone alone diminished in time.	4

Based on these results a number of recommendations can be made in patients who need maintenance treatment for opioid use disorder, if a drug without opioid agonistic properties is preferred (table 3). These recommendations have been hierarchized according to the GRADE system [35].

Regarding the limitations of current review it can be mentioned the overall low quality design of the clinical research, only 13 articles included double-blind, controlled, randomized trials. Another limitation is related to the low number of drugs investigated, and except for naltrexone (oral and extended-release), data regarding the efficacy or tolerability of other pharmacological agents were derived from few good quality trials. Only one reviewer was involved in the processing of data collected, so a bias related to this

aspect can not be excluded. More research is needed, and larger, well designed trials focused on a more diverse range of drugs are also expected to be launched in order to provide more accurate recommendation in a continuously extending pathology, like the opioid use disorder.

Table 3. Recommendation based on the literature review for patients with opioid use disorder with non-opioid agonist pharmacological agents

Treatment	Clinical trials	Advantages/disadvantages	GRADE recommendations
Naltrexone- oral administration	[9-15]	(+) naltrexone improve depressive symptoms in patients with opioid use disorder at 6 months (+) naltrexone plus fluoxetine and individual psychotherapy has been proven useful in women with heroin dependence (+) naltrexone plus gabapentin improved muscle pain and psychological dependence severity in patients dependent on pentazocine (+) naltrexone plus sertraline increased short-term treatment retention of recently non-depressed opioid abstinent patients (-) buprenorphine/naloxone was superior to naloxone in the reduction of opioid-positive urine test and preserving patients participation in the treatment (-) similar weight gain during 6 months of treatment when compared to methadone (-) naltrexone was inferior to buprenorphine (not statistically significant) in several outcomes regarding the rate of relapse in detoxified heroin dependent patients	B
Naltrexone- extended release	[16-23]	(+) efficacy and tolerability were similar to buprenorphine/naltrexone (+) lower rate of relapse when compared to treatment as usual, at least on short-term (+) better outcomes than those treated with oral formulation of the same drug (+) naltrexone implants but not methadone were associated with long-term benefits in decreasing opioid-related hospital morbidity (+) efficient in preventing opioid overdose (+) improved depression severity at 4 weeks post-baseline (+) improved quality of life, rate of retention, opioid-negative urines, opioid craving, rate of re-employment (+) prolonged the duration of abstinence to opioids, in combination with counselling (-) worsened late insomnia (-) requires implant of the active drug (usually subcutaneous)	B+
Topiramate	[25]	(-) negative results in patients with opioid and cocaine use disorder	D-
Ibudilast	[26]	(+) induced lower rates of drug liking (oxycodone), lower craving to heroin/tobacco/cocaine and lower subjective ratings of pain vs. placebo	C
Memantine	[29-32]	(+) may provide an easier transition to buprenorphine-free therapeutic regimen (+) induced attenuation of chronic opioid-dependence-related cognitive impairment (+) decreased the daily dose of methadone (+) it had positive effect over probably NMDA-mediated inflammatory processes in opioid users (+) it decreased the subjective effects of heroin in chronic users (-) it did not decreased the reinforcing effects of heroin in non-treatment seeker heroin-dependent patients	C+

Treatment	Clinical trials	Advantages/disadvantages	GRADE recommendations
Dronabinol	[34]	(+) it decreased the severity of opioid withdrawal (-) no effect over rates of naltrexone-treatment induction or retention	D
Dextro-methorphan	[37-39]	(+) it was useful in low doses as adjuvant treatment in methadone-treated patients both at inflammatory level and clinical level (+) the quality of life was superior in patients who received dextromethorphan as adjuvant to methadone versus placebo plus methadone (-) the difference versus placebo was not significant in the otcome defined as mean methadone consumption	C
Olanzapine	[40,41]	(+) it reduced direct aggressiveness, overall hostility, verbal aggressiveness, and aggressive incidents (+) improved the rate of treatment retention	C
Buspirone	[43]	(+) positive effect over depressive symptoms associated to methadone maintenance treatment (-) no effect over anxiety	C-
Baclofen	[45]	(+) significantly better treatment retention	C-

From the data collected in this review only extended release naltrexone seems to achieve a B+ level of recommendation, based on 8 trials, and the benefits of using extended-release naltrexone tend to overcome its potential disadvantages in patients with opioid use disorder who underwent successful disintoxication. This naltrexone formulation had positive impact over a large number of outcomes related to opioid use disorder, including rate of relapse, quality of life, opioid-related hospital morbidity, and depressive severity [16-23]. As an alternative, oral naltrexone may be tried, although negative trials exist – level B recommendation, based on 7 trials [9-15]. Naltrexone plus fluoxetine and individual psychotherapy has been proven a useful combination especially in women with heroin dependence [15]. Naltrexone plus gabapentin improved muscle pain and psychological dependence severity in patients dependent on pentazocine [13]. Naltrexone plus sertraline were well-tolerated and increased on short-term treatment retention of recently non-depressed opioid abstinent patients [14].

Memantine has a level C+ recommendation for its use as adjuvant treatment in opioid use disorder because there more data to support its efficacy are needed. Low dose memantine attenuated chronic opioid-dependence-induced cognitive impairment and decreased the daily dose of methadone [30, 31]. However, information have been gathered about its positive effect over cognition, inflammatory processes, and decrease of methadone daily dose [29-32].

Olanzapine may be recommended for controlling aggressivity in patients with opioid use disorder, as adjuvant treatment (level C) [40, 41].

Dextromethorphan was associated with some positive results, although it did not decrease the necessary daily dose of methadone when used as adjuvant agent [37-39]. This drug was however useful in improving both clinical and inflammatory outcomes, and improved patients' quality of life [37-39].

Dronabinol did not prove itself efficient in the maintenance phase of treatment, although it may be of some help in alleviating withdrawal symptoms in opioid users [34].

Data for ibudilast, baclofen, and buspirone are insufficient to allow for stronger recommendations in the targeted population, but further research may change this perspective.

CONCLUSIONS

Data showing a continued increase of illegal opioids use are overwhelming, and it became obvious that clinicians must find new solutions for treating a continuously growing population affected by opioid

use disorder. Opioid agonists like buprenorphine and methadone are considered now the first line for treatment of opioid dependent patients, but non-opioid agonist drugs should be investigated more, either as adjuvant agents or as monotherapy. These non-opioid agonist agents can lead to the administration of lower doses of opioid agonists (in case of adjuvant treatment), or even to their complete replacement, in both cases diminishing the risk for a new dependence.

From the data reviewed, extended-release naltrexone is the most supported by evidence recommendation, followed by oral naltrexone, in patients who were successfully detoxified from opioids. Naltrexone had positive results not only on the opioid use-related outcomes, but also over associated symptoms, like depression.

As adjuvant agents, olanzapine may be efficient for aggressive behaviours in opioid dependent patients, memantine could improve cognitive function and decrease the inflammatory processes associated with substance use disorders, and dextromethorphan may also help decreasing the inflammatory processes. Further research is needed in order to verify the efficacy and tolerability of olanzapine, memantine and dextromethorphan as adjuvant agents.

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