Addiction

REVIEW

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Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence

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ABSTRACT

Aim The goal of this systematic review was to identify moderators of naltrexone efficacy in the treatment of alcohol dependence. **Methods** We searched Pubmed, CINHAL, Embase, PsycINFO and the Cochrane Library from 1990 to April 2012 and reference lists of pertinent review articles, which yielded 622 trial, pooled analysis and review articles. Using pre-established eligibility criteria, two reviewers independently determined whether abstracts contained evidence of demographic or biological characteristics, i.e. moderators, influencing naltrexone response in alcohol dependence. We assessed each publication for risk of bias and evaluated the strength of the body of evidence for each moderator. **Results** Twenty-eight publications (on 20 studies) met criteria for data synthesis. These included 26 publications from 12 randomized, placebo-controlled trials, three non-randomized, non-placebo studies and one randomized, non-placebo study. In addition, there were two publications from pooled analyses of four randomized, placebo-controlled trials. Family history of alcohol problems and the Asn40Asp polymorphism of the μ-opioid receptor gene showed a positive association with efficacy in four of five and three of five studies, respectively. Other moderators reported to be associated with efficacy included male sex (two of five studies), pre-treatment drinking (two of two studies) and high craving (two of five studies). However, the overall risk of bias in the published literature is high. **Conclusions** The identification of naltrexone-responsive alcohol-dependent patients is still in development. Studies to date point to two potential moderators—family history and presence of the OPRM1 Asn40Asp polymorphism—as having the strongest evidence. However, the data to date is still insufficient to recommend that any moderator be used in determining clinical treatment.

Keywords Alcohol dependence, craving, family history, naltrexone, moderators, OPMR1 Asn40Asp polymorphism.

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INTRODUCTION

Alcohol dependence is a prevalent illness with life-time and 12-month prevalence rates in the United States of 12.5 and 3.8%, respectively [1]. Alcohol dependence and excessive alcohol use are costly, both in economic terms [2] and in lives lost [3]. However, only a minority of patients with alcohol dependence receive psychosocial, pharmacological or both treatments—in the order of fewer than 25% [1]. This is unfortunate, as the treatment of alcohol dependence can be very effective [4].

In 1994, naltrexone, a non-specific opioid antagonist, was approved by the Food and Drug Administration for the treatment of alcohol dependence. The most consistent effect of naltrexone reported in clinical trials has been a reduction in relapse to heavy drinking [5], but reductions in heavy drinking days, overall drinking and craving have been noted [6].

Despite the evidence of the efficacy of naltrexone for alcohol dependence, its use has been limited [7]. This may be due to a perceived sense of minimal efficacy, as treatment effect sizes have been reported to be in the low

range—0.12 comparing naltrexone to placebo on percentage of abstinence and –0.16 indicating the placebo group had a greater relapse rate to heavy drinking [8,9].

Medications that demonstrate some degree of efficacy in an overall population of alcohol-dependent individuals might show much better efficacy if the 'right' subgroup of patients could be identified by assessing moderators such as age or gender (see Kraemer *et al.* [10] and Wallace *et al.* [11]). Indeed, work has begun to investigate potential moderators of response to naltrexone in alcohol dependence, e.g. the μ-opioid receptor gene (OPRM1) Asn40Asp polymorphism (see Chamorro for review [12]). Accordingly, the current manuscript provides a systematic review of the world literature on clinical and biological moderators of naltrexone response in alcohol dependence to evaluate the current status of the literature and the strength of evidence for the various moderators.

MATERIALS AND METHODS

Data sources and searches

We searched the PUBMED, CINAHL, EMBASE and PsycINFO databases and the Cochrane Library from 1990 to April 2012, using Medical Subject Headings when available or key words when appropriate. We combined terms for alcoholism, drinking behaviors and similar terms with generic and brand names for naltrexone; we also included key words for drinking outcomes, harms, and psychiatric comorbidities. We limited electronic searches to 'adult', 'human' and 'English language'. We also performed manual searches of reference lists of pertinent review articles.

Study eligibility

Two members of the research team independently reviewed abstracts and full-text publications. Inclusion criteria stipulated that studies examine the efficacy or effectiveness of naltrexone treatment for adults with alcohol disorders or alcohol problems treated in in-patient or out-patient settings. We required that at least 90% of the study population meet the DSM (III or IV), ICD-9 CM or ICD-10 criteria for alcohol dependence. We did not include trials that focused on a comorbid condition such as cocaine dependence or depression. All studies had to include one of two designs: (i) naltrexone to placebo and presence of moderator to absence of moderator or (ii) naltrexone in the presence of moderator to naltrexone in the absence of moderator. We included open-label and blinded randomized controlled trials (RCTs), non-randomized controlled trials, prospective and retrospective cohort studies and case–control studies with sample size ≥30 patients and laboratory studies of any sample size.

We evaluated only the factors that would inform clinical decision-making with regard to initiating treatment, not factors that would affect the outcome of treatment once therapy began, such as adherence to treatment. Similarly, we did not include studies evaluating administration schedule, formulation (tablet versus depot), duration of use or adverse events as moderators. We considered adjunctive psychosocial or pharmacological treatments as outside the scope of this review.

We excluded publications that both reviewers agreed did not meet eligibility criteria. Investigators resolved disagreements by consensus or by consulting a third senior reviewer.

Data extraction, risk of bias and synthesis

We designed structured forms to extract pertinent information from each publication, including items relevant for assessing risk of bias. We extracted all relevant information on moderators and alcohol outcomes in which the analyses were specific to naltrexone. All data extractions were reviewed for completeness and accuracy by a second research team member.

To assess the risk of bias (internal validity) of studies, we used predefined criteria based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews (ratings: low, medium, high) [13].

Because the heterogeneity of the populations, comparators and outcome measures did not allow for a pooled analysis, we conducted only qualitative analyses. To develop our summary tables (Tables 1–5), we summarized the findings for a moderator across all the drinking outcomes available in each publication. We present a summary table for each moderator assessed in at least three publications, even if the publications were derived from the same study. We discuss moderators addressed in two publications in text only; we do not summarize results for moderators addressed by only a single publication.

For the summary tables, if there was at least one significant association ($P \leq 0.05$) for a moderator in one direction (i.e. negative or positive) for any drinking outcome and no other significant contradictory associations, the significant association was used to define whether the naltrexone response was positively (↑) or negatively (↓) associated with the moderator. We used ↔ to indicate that there were no significant associations or if the evidence was mixed.

Rating strength of evidence

We evaluated the strength of evidence for each major moderator using a modified GRADE (Grading of

Recommendations Assessment, Development and Evaluation) approach [14]. Considering all included studies for a moderator, we assessed four domains: risk of bias (study limitations increasing the likelihood of inadequate protection against bias); directness (whether evidence links interventions directly to a health outcome of importance for the review); consistency (degree to which studies found either same direction or similar magnitude of effect); and precision (degree of certainty surrounding an effect estimate based on sufficiency of sample size and number of events). We used the individual domain scores to form an overall strength of evidence grade (high, moderate, low, insufficient) corresponding to the confidence the team had that the evidence reflects the true effect (i.e. a true association between the moderator and naltrexone's effectiveness).

RESULTS

Results of literature searches

Our searches of databases and reference lists identified 622 citations (Fig. 1). We obtained 158 publications for full text review. Twenty-eight publications (on 20 studies) met criteria for data synthesis. These included 26 publications from 12 randomized, placebo-controlled trials, three non-randomized, non-placebo studies and one randomized, non-placebo study. In addition, there were two publications from pooled analyses of four randomized, placebo-controlled trials.

Family history of alcohol dependence/abuse

Five studies (four analyses of results from clinical trials and one from a laboratory trial) examined family history (Table 1). Four studies found evidence for an association between a positive family history and response to naltrexone [15–18]. Rubio *et al.* [16] found that participants with a first-degree family history of alcoholism did significantly better on naltrexone than those treated with psychotherapy alone, whereas there was no effect of naltrexone in those without a positive family history. Two of the studies found the greatest difference in the reduction of heavy drinking between naltrexone and placebo in those with a higher percentage of family members with alcohol problems [15,17]. In a laboratory study, Krishnan-Sarin *et al.* [18] found that 100 mg of naltrexone reduced drinks consumed over a 2-hour period only in those with a first-degree relative with alcoholism. Conversely, a re-analysis of the COMBINE data by Capone *et al.* [19] reported no significant interaction for family history and naltrexone response for percentage of days abstinent, drinks per drinking day and percentage of heavy drinking days.

Pre-treatment craving for alcohol

Three of five studies examining the influence of pre-treatment craving on naltrexone response found no significant association (Table 2) [20–22]. Conversely, two studies, Monterosso *et al.* [15] and Jaffe *et al.* [23] reported evidence that high levels of baseline craving were associated with reductions in drinking with naltrexone compared to placebo.

Asn40Asp polymorphism of the OPRM1 and other genetic markers

Four of six publications (from five studies), with one using a haplotype analysis, reported a positive relation between

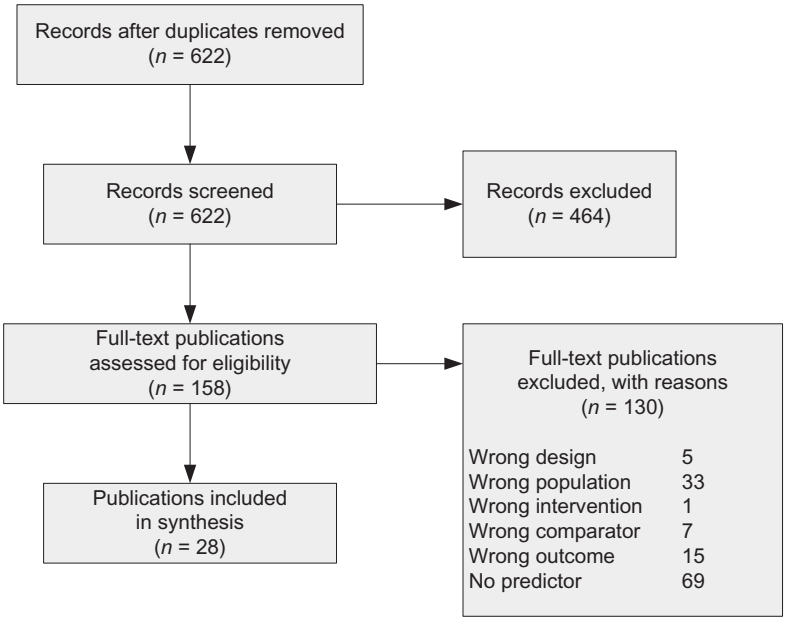

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram: summary of search and selection

Table 1 Relation of family history of alcoholism/alcohol problems to response to naltrexone.

Author, year	*Study design* *Type of analysis* *Duration*	*Interventions*	*Sample size*	*Findings*
Capone *et al.*, 2011 [19] COMBINE	Subgroup modeling analysis from RCT 16 weeks	NTX 100 mg/day and/or acamprosate 3g/day Placebo	603	↔
Monterosso *et al.*, 2001 [15]	RCT 12 weeks	NTX 50–100 mg/day Placebo	179 Percentage with an alcohol problem • ≤25%: 77 • 25–50%: 73 • ≥50%: 29	↑
Rohsenow *et al.*, 2007 [17]	*Post-hoc* analysis of RCT 12 weeks	NTX 50 mg/day Placebo	112 Family history percentage: • None (0%): 21 • Low (<20%): 41 • High (≥20%): 50	↑
Rubio *et al.*, 2005 [16]	Open-label RCT, no placebo 12 weeks	NTX 50 mg/day Control (psychotherapy only)	216 Family history positive: • NTX: 104 • Control: 112	↑
Krishnan-Sarin *et al.*, 2007 [18]	Laboratory RCT *post-hoc* analysis 6 days	NTX 50 mg/day NTX 100 mg/day Placebo	92 Family history positive: • NTX 50: 12 • NTX 100: 14 • Control: 12	↑ In 100 mg/day only

COMBINE = Combined Pharmacotherapies and Behavioral Interventions; NTX = naltrexone; RCT = randomized con-trolled trial. Thick black line denotes laboratory studies below.

Table 2 Relation of pre-treatment craving for alcohol to response to naltrexone.

Author, year	*Study design* *Type of analysis* *Duration*	*Interventions*	*Sample size*	*Findings*
Garbutt *et al.*, 2009 [22]	Non-randomized open-label study, no placebo 12 weeks	NTX 50 mg/day	40	↔
Guardia *et al.*, 2002 [20]	RCT 12 weeks	NTX 50 mg/day Placebo	192	↔
Jaffe *et al.*, 1996 [23]	RCT 12 weeks	NTX 50 mg/day Placebo	58 Higher versus lower baseline craving levels	↑
Kiefer *et al.*, 2005 [21]	Secondary analysis of RCT 12 weeks	NTX 50 mg/day NTX 50 mg/day and acamprosate 1998 mg/day Placebo	143	↔
Monterosso *et al.*, 2001 [15]	RCT 12 weeks	NTX 50–100 mg/day Placebo	173 Craving level • Low: 44 • Moderate: 72 • High: 57	↑

NTX = naltrexone; RCT = randomized controlled trial.

Table 3 Relationship of the Asn40Asp polymorphism to response to naltrexone.

Author, year	*Study design* *Type of analysis* *Duration*	*Interventions*	*Sample size*	*Findings*
Anton *et al.*, 2008 [24] COMBINE	RCT 16 weeks	NTX 100 mg/day Placebo	307 Medical management only Asn40 (P): 126 Asn40 (N): 115 Asn40Asp (P): 35 Asn40Asp (N): 31	↑[a]
Oroszi *et al.*, 2009 [25]	Caucasians with data for either the OPRM1 block 1 or block 2 haplotype who did not receive CBI	NTX 100 mg/day[b] Placebo	306[c] Asn40 (P): 107 Asn40 (N): 97 Asn40Asp (P): 25 Asn40Asp (N): 20	↑
Coller *et al.*, 2011 [29]	Non-randomized open-label study 12 weeks	NTX 50 mg/day	100 Asn40: 65 Asp 40: 35	↔
Gelernter *et al.*, 2007 [28]	Substudy of VA RCT 12 months	NTX 50 mg/day Placebo	220 Asn40 (P): 50 Asn40 (N): 98 Asn40Asp (P): 9 Asn40Asp (N): 33	↔
Kim, *et al.*, 2009 [26]	Non-randomized study 12 weeks	NTX 50 mg/day	32[d] Asn40: 16 Asn40Asp: 16	↑
Oslin *et al.*, 2003 [27]	Pooled analysis of 3 RCTs 3–9 months	NTX 50–100 mg/day Placebo	130 Asn40 (P): 41 Asn40 (N): 48 Asn40Asp (P): 18 Asn40Asp (N): 23	↑

CBI = cognitive behavioral intervention; NTX = naltrexone; RCT = randomized controlled trial; OPRMI1 = μ-opioid receptor gene; COMBINE = Combined Pharmacotherapies and Behavioral Interventions. Dashed line between two studies indicates analyses from the same trial. [a]Positive treatment response for percentage of days abstinent found in naltrexone group with medical management only, not in those who received medical management with cognitive behavioral intervention. [b]Authors grouped patients based on whether they received active naltrexone or placebo, regardless of whether or not they received acamprosate. [c]Only the three most common diplotypes are enumerated. [d]Adherent patients only.

the presence of one or two copies of the OPRM1 Asn40Asp allele and naltrexone response (Table 3) [24–27]. In a pooled analysis of three trials, Oslin *et al.* [27] reported that those with the Asn40Asp allele who received naltrexone had lower relapse rates than those without the allele (no effect was found in the placebo group). Using data from the COMBINE trial, Anton *et al.* [24] found a significant genotype × medication interaction ($P = 0.005$)—subjects with the OPRM1 Asn40Asp allele were more likely to have a good clinical outcome when treated with naltrexone compared to placebo, whereas those without this allele did not show a naltrexone/placebo difference. In an open-label trial comparing OPRM1 Asn40Asp carriers to non-carriers, Kim *et al.* [26] found a longer time to relapse in the OPRM1 Asn40Asp carriers who were adherent to treatment. Conversely, Gelernter and colleagues [28] reported no effect of the Asn40Asp polymorphism on naltrexone response and did not find any significant effect for other single nucleotide polymorphisms in genes encoding the μ (OPRM1), δ (OPRD1) or κ (OPRK1) opioid receptors. Similarly, Coller *et al.* [29], in an open-label trial comparing OPRM1 Asn40Asp carriers to non-carriers, found no association between OPRM1 Asn40Asp genotype and improvement on drinking outcomes. Additionally, Oroszi *et al.* [25] did not find any associations to naltrexone response with genetic variants in OPRM1 other than the Asn40Asp polymorphism.

Regarding other genetic markers, Kiefer *et al.* [30] analyzed an intronic single nucleotide polymorphism (SNP) in the gene for GATA-binding protein 4 (GATA4), which may affect atrial natriuretic peptide. They did not find a relationship between this SNP and naltrexone response.

Sex

Six studies (in seven publications) evaluated sex as a moderator of naltrexone response (Table 4) [19,31–36]. Three analyses of the COMBINE data showed no evidence of differential naltrexone response by sex for any drinking outcomes [19,31,32]. Investigators noted that the study was not powered to detect small to moderate differences in treatment effects by sex. A pooled analysis of data from two 12-week RCTs found similar results [33]. Differences between naltrexone and placebo within men were significant, but not within women, although effect sizes were similar. One *post-hoc* exploratory analysis of an RCT found a positive association in naltrexone-treated women but no such response in men [35]. Two studies showed a positive effect for naltrexone in men, but not in women [34,36].

Pre-treatment drinking

Two publications [34,37] from one trial [34] reported that pre-treatment abstinence improved naltrexone response (Table 5). Garbutt *et al.* [34] found that subjects who achieved 7 or more days of abstinence prior to randomization had significantly fewer heavy drinking days with long-acting naltrexone compared to those who had not achieved at least 7 days of abstinence. A *post-hoc* analysis of this study focusing on participants with 4 or more days lead in abstinence found similar results [37].

Gueorguieva *et al.* [38,39], using data from COMBINE and focusing on those randomized to naltrexone, found that certain trajectories of drinking before starting naltrexone affect response, but the nature of the trajectories is not straightforward.

Other factors

In a secondary subgroup analysis of data from the Veteran Affairs Cooperative Study that focused on those diagnosed with mood or anxiety disorders, Krystal *et al.* [40] found no association between Brief Symptom Inventory (BSI) scores and naltrexone response. In contrast, Kiefer *et al.* [21], reported that naltrexone-treated participants with high baseline Symptom Checklist scores (SCL-90) had a significantly longer time to first drink than those with low baseline scores. Further, participants with baseline depression scores higher than the median had significantly better responses to naltrexone than those with low scores.

Three publications assessed the relation between alcohol typology and naltrexone response [16,21,41],

Table 4 Relationship of sex to response to naltrexone.

Author, year	*Study design* *Type of analysis* *Duration*	*Interventions*	*Sample size*	*Findings*
Anton, *et al.*, 2006 [31] COMBINE	RCT 16 weeks	NTX 100 mg/day and/or acamprosate 3g/day Placebo	1226 (848 men)	↔
Capone *et al.*, 2011 [19] COMBINE	Subgroup modeling analysis	NTX 100 mg/day and or acamprosate 3 g/day Placebo	603 (416 men)	↔
Greenfield *et al.*, 2010 [32] COMBINE	Secondary analysis	NTX 100 mg/day and/or acamprosate 3 g/day Placebo	1226 (848 men)	↔
Baros *et al.*, 2008 [33]	Pooled data *post-hoc* subgroup analysis from 2 RCTs 12 weeks	NTX 50 mg/day Placebo	211 (154 men)	↔
Garbutt *et al.*, 2005 [34]	RCT 6 months	NTX XR 190 mg/month NTX XR 380 mg/month Placebo	624 (423 men)	↑ For men (380 mg only)
Kiefer *et al.*, 2005 [35]	RCT *post-hoc* exploratory analysis 12 weeks	NTX 50 mg/day Placebo	80[a] (58 men)	↑ For women
Kranzler *et al.*, 2009 [36]	RCT 12 weeks	NTX 50 mg/day or 50 mg targeted dose Placebo	163 (95 men)	↑ For men

Dashed line between two studies indicates analyses from the same trial. [a]Does not include those randomized to acamprosate only and to combination (naltrexone + acamprosate). COMBINE = Combined Pharmacotherapies and Behavioral Interventions; NTX = naltrexone; RCT = randomized controlled trial.

Table 5 Relationship of pre-treatment drinking to response to naltrexone

Author, year	*Study design* *Type of analysis* *Duration*	*Interventions*	*Sample size*	*Findings*
Garbutt *et al.*, 2005 [34]	RCT 24 weeks	NTX XR 190 or 380 mg/month Placebo	624 (53 with lead-in abstinence[a])	↑ Lead-in abstinence
Pettinati *et al.*, 2011 [37]	*Post-hoc* subgroup analysis of Garbutt 2005	NTX XR 380 mg/month Placebo	196 (19 with lead-in abstinence[b])	↑ Lead-in abstinence
Gueorguieva, *et al.*, 2011 [38] COMBINE	RCT secondary subgroup analysis 12 weeks	NTX 100 mg/d Placebo	1226	↑ Drinking trajectory intermediate between frequent and daily drinking

Dashed line between two studies indicates analyses from the same trial. [a]Abstinence for 7 days prior to randomization. [b]Abstinence for ≥4 days prior to randomization. COMBINE = Combined Pharmacotherapies and Behavioral Interventions; NTX = naltrexone; RCT = randomized controlled trial.

but there was substantial heterogeneity in typological classifications, (i.e. Cloninger typology, Babor typology, Lesch typology and age of onset of habitual consumption). In an analysis of COMBINE data, Bogenschutz *et al.* [41] reported an interaction between Babor typology and naltrexone response for percentage of heavy drinking days. Type A (later onset, less severe, no conduct disorder) naltrexone-treated participants who received medical management without cognitive behavioral intervention (CBI) had a better treatment response than type B participants; the authors did not find an interaction between age-of-onset and response to naltrexone. Kiefer *et al.* [21] found that Cloninger type I alcoholics treated with naltrexone, acamprosate or a combination of the two medications had a longer time to first drink and relapse compared to Cloninger type II alcoholics, although the results were not statistically significant. Similarly, naltrexone-treated Lesch types III and IV alcoholics had a longer time to first drink and first relapse than naltrexone-treated Lesch types I or II alcoholics [21]. Rubio *et al.* [16] reported that the onset of alcohol problems before the age of 25 years was associated with a better naltrexone response.

Two studies examined the impact of the sweet-liking/sweet-disliking phenotype on naltrexone response [22,42]. In an open trial, Garbutt *et al.* [22] reported that in those with the sweet-liking phenotype, the higher their craving for alcohol the better they did on naltrexone, whereas those with the sweet-disliking phenotype did worse as craving increased. Laaksonen *et al.* [42] reported that, in naltrexone-treated participants, as sweet liking increased, relapses to heavy drinking decreased, whereas relapses increased for those treated with placebo.

Other factors addressed by single publications and so not described in the results include smoking, non-verbal learning ability, age, pre-treatment alcohol dependence severity, occupation and marital status.

In Fig. 2 we show the findings of the systematic review using a fishbone diagram [43]. This graphic captures the relationship of tested moderators to naltrexone response.

Risk of bias

We assessed risk of bias by explicitly evaluating risk of selection, performance, attrition and detection biases. We did not identify any well-designed trials with the primary objective evaluating moderators of naltrexone response. Most analyses of moderators were *post hoc* or exploratory in nature. Other reasons for high risk of bias included overall high attrition, high differential attrition, inadequate method of randomization, insufficient power and lack of intention-to-treat analysis.

Strength of evidence

Strength of evidence for each moderator was low. Given the overall deficiencies of included studies and the small number of studies addressing each moderator, we had low confidence that the evidence for any moderator reflects the true effect.

DISCUSSION

This systematic review aimed to identify moderators of response to naltrexone, a medication that has been shown to reduce heavy drinking and enhance the likelihood of abstinence. A careful review of the quality of the evidence was another important element of the review.

The most salient aspect of the review and perhaps the key finding is that the overall strength of evidence in support of individual moderators of response to

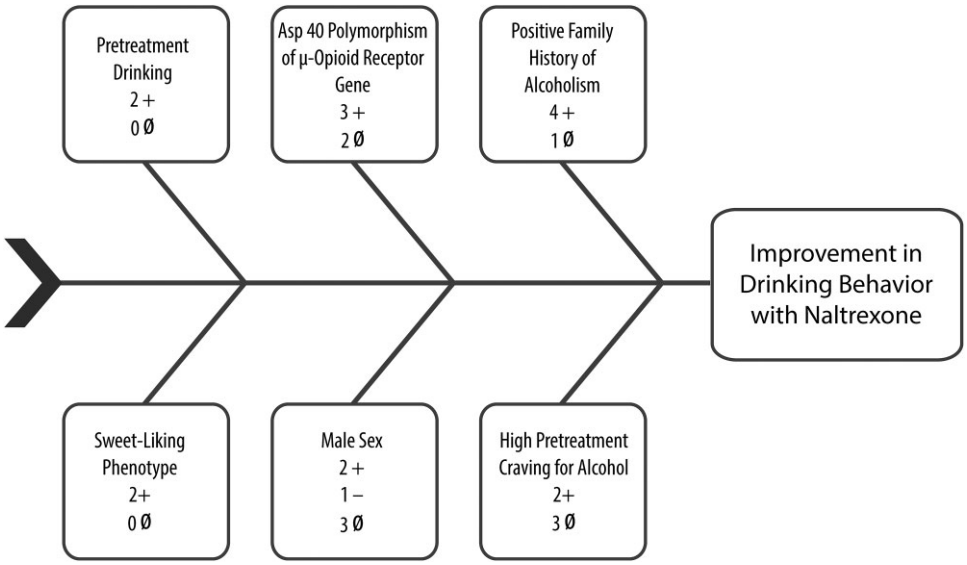

Figure 2 Fishbone diagram of possible moderators of response to naltrexone in alcohol dependence. For each bone, we provide the number of studies that indicate a positive (+) or negative (–) association or mixed/neutral evidence (ø) between the moderator and naltrexone response

naltrexone is weak. As noted in methods, we utilized standard approaches to assess both the risk of bias and the strength of evidence. This approach evaluates both the quality of the individual studies and the preponderance of evidence. The reason we conclude that the risk of bias is relatively high and the strength of evidence is low is based on several points. Very few studies used an a priori hypothesis with a prospective design, many studies were secondary analyses and many studies were on subsets of individuals selected from a clinical trial designed to examine overall efficacy of naltrexone rather than a moderator of naltrexone response. There was considerable variance in the how investigators defined the characteristic of interest, e.g. family history and craving, such that comparing across studies was difficult. In many instances, several of these problems were present in one study.

Therefore, an important conclusion from this systematic review is that efforts to identify moderators of naltrexone response need to move towards designing prospective trials on clearly defined moderators using adequate power with appropriate statistical methods.

Even with the methodological weaknesses noted above, the reviewed data provide evidence for variability in naltrexone response that may be amenable to the development of prospective identification at the individual level, fostering personalized medicine.

The two factors with the most consistent evidence of potential value as a predictor of naltrexone response are the OPRM1 Asn40Asp polymorphism of the u-opioid receptor and family history of alcoholism—it should be noted these are not synonymous moderators. Four of the six publications investigating the OPRM1 Asn40Asp polymorphism reported a significant positive association for naltrexone response, although two of these publications [24,25] evaluated the same population. Furthermore, since April, 2012 (when we conducted our update search), at least three studies have been published examining the Asn40Asp polymorphism and response to naltrexone. Kranzler *et al.*[44] found no main effect of medication, genotype or their interaction on drinking but a significant three-way interaction between medication × genotype × daily desire to drink. Anton *et al.* [45,46] did not find a main effect of naltrexone or the OPRM1 genotype on drinking behavior, but did find evidence that the OPRM1 Asn40Asp SNP was associated with less neural activation to alcohol cues with naltrexone. Additionally, for both drinking and neural activation there was evidence for an interaction between naltrexone, OPRM1 Asn40Asp and variations in the dopamine transporter gene (SLC6A3). The OPRM1 Asn40Asp polymorphism may confer altered opioid and enhanced dopamine responses to alcohol (see Ramchandani *et al.* [47]). The hypothesis has been put forward that this enhanced response predicts a greater effect for the opioid antagonist naltrexone, and thus the OPRM1 Asn40Asp polymorphism predicts treatment response. However, despite the evidence of a positive signal for this predictor (see also Chamorro *et al.* [12]), the overall strength of evidence is considered insufficient. The two ongoing prospective trials (ClinicalTrials.gov ID #NCT00920829 and #NCT00831272) designed to evaluate the OPRM1 Asn40Asp polymorphism should significantly advance our understanding but, for now,

it is premature to recommend this marker for clinical practice.

Four of five studies found evidence that a positive family history of alcoholism is associated with a positive response to naltrexone. A key issue with this body of evidence is that establishing the presence of a positive family history is not straightforward. For example, different definitions have been used—a simple yes/no for noting first-degree relatives with alcohol problems, the percentage of relatives with a positive drinking history, or other descriptions. If family history proves to be an important predictor of naltrexone response it will need to be operationalized for clinical use, perhaps by employing a standardized instrument such as the Family History of Alcoholism Module [48].

Craving for alcohol had been suggested as a predictive factor for naltrexone response dating back to the early reports of Monterosso *et al*. [15] and Jaffe *et al*. [23]. However, the data in support of craving as a predictor is not strong, with only these two studies, of five that evaluated craving, reporting a relationship between high craving for alcohol and naltrexone response. Assessing craving through more sophisticated means such as neuroimaging may provide a more powerful method, but would not represent a practical clinical approach.

Sex (male) and pre-treatment drinking were other factors showing a potential signal for predicting a positive naltrexone response, whereas alcoholism subtype has been insufficiently studied. Factors were primarily considered independent of one another and, therefore, how factors might relate to one another or be combined to increase predictive power is not known, but represents a potentially fruitful direction for future research [11].

Applicability and study limitations

We considered the applicability of the individual studies and assessed applicability across the body of evidence. Most of the studies focused on Caucasian men, so women and racial minorities are under-represented, which can also impact upon genetic studies. Additionally, recruitment was often by advertisement, so the applicability to patients with alcohol dependence seeking treatment in traditional settings is probably impacted. In addition, the inclusion and exclusion criteria often required that none of the participants have a comorbid psychiatric disorder that is distinctly different from the clinical setting. The comparator groups varied extensively across all the studies, with some studies only having a psychosocial therapy as the comparator and others having adjunctive treatments and/or placebo along with the psychosocial therapy. Furthermore, the type of psychosocial intervention varied across trials and adds additional complexity when comparing trials. For example, in the COMBINE trial [31] a naltrexone effect was not clear in the presence of more intense psychosocial therapy, so therapies may obscure moderator effects on naltrexone. Additionally, we reviewed oral and intramuscular naltrexone together, although the formulations' differing pharmacokinetic profiles might affect the impact of a predictor. Also, identification of a moderator requires that a trial detect a naltrexone effect and that is not always the case; and, of course, negative moderator trials may not have been published. All these factors contribute to the heterogeneity of treatment effect noted and further weaken our ability to generalize about various moderators of naltrexone response.

In summary, the current systematic review for predictors of response to naltrexone in alcohol dependence revealed that the strength of evidence for any predictive factor is low or insufficient. Researchers should continue to identify robust factors associated with naltrexone response in alcohol dependence; such efforts have the potential to significantly improve pharmacological management for the alcohol-dependent patient and truly provide personalized medicine.

Declaration of interests

J.C.G., A.M.G. S.L.W., L.C.M., H.S.J. and G.V.B. report no biomedical financial interests or potential conflicts of interest. A.K.-P. is listed on a patent for the use of oxytocin for alcohol dependence and other substance use disorders.

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