Summary Report

Disulfiram

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
AUD	Alcohol use disorder
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of disulfiram (UNII code:TR3MLJ1UAI), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how disulfiram is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how disulfiram has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of disulfiram and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Disulfiram was nominated for inclusion on the 503B Bulks List by Alfonse Muto for alcohol addiction via a 250 mg/mL intramuscular injection solution in a single dose vial.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of disulfiram.[6-17]

Reasons provided for nomination to the 503B Bulks List included:

- The only approved disulfiram product available is in the form of tablets. The tablets may have additional excipients that are unnecessary and could potentially affect the product quality and/or produce unwanted affects in patients. Excipients in the brand name Antabuse product include silicone dioxide, anhydrous lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate type A potato, and stearic acid. These excipients may affect product solubility, making it difficult to reach the desired 250 mg/mL concentration.
- Compared to Antabuse (oral disulfiram), the compounded injection allows for a unique depot effect based on pharmacokinetic properties such as allowing for a continuous uniform flow of drug into the bloodstream. Bioavailability is also increased as an injectable, which permits a smaller dosage, decreases patient exposure to the drug, and decreases dosing frequency to monthly (compared to daily oral administration). This could increase adherence and efficacy in patients. The injectable form is also associated with a decrease in side effects like liver concerns.
- Per the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), the injection form provides better therapeutic remission as compared to oral administration.
- Compared to Vivitrol's (extended-release naltrexone injectable suspension) concentration in the bloodstream, which starts to decline within 14 days of administration, the disulfiram injection can provide uniform drug concentrations in the bloodstream for one month. Disulfiram has a positive effect on the mental condition of alcohol dependent patients while naltrexone is an antidote, so alcohol craving return is high for patients treated with it. Disulfiram also has a more favorable side effect profile than naltrexone.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of disulfiram products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for disulfiram; name variations of disulfiram were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing disulfiram. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: disulfiram, injectable administration, and therapeutic use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to original human studies in English language. Searches were conducted on March 9, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 9, 2020 for clinical practice guidelines that recommended the use of disulfiram and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which disulfiram was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design);

designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if disulfiram was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which disulfiram was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of disulfiram; setting; total number of patients; number of patients who received disulfiram; patient population; indication for use of disulfiram; dosage form and strength; dose; ROA; frequency and duration of therapy; use of disulfiram in a combination product; use and formulation of disulfiram in a compounded product; use of disulfiram compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances disulfiram was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use disulfiram: primary care and internal medicine, and psychiatry. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of disulfiram in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the

identified persons. Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Disulfiram is not available as an FDA-approved product in the nominated dosage form and ROA.
- Disulfiram is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for disulfiram.
- Disulfiram is not available in the nominated dosage form and ROA in any of the foreign medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 334 references; 3 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 310 titles and abstracts were screened. After screening, the full text of 48 articles was reviewed. Finally, 0 studies were included. Forty-eight studies were excluded for the following reasons: wrong study design (33 studies); wrong dosage form or ROA (8); disulfiram only mentioned briefly (6); disulfiram used as brand or proprietary product (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

No studies were included from the literature review.

Use of disulfiram

No studies were included from the literature review.

Pharmacology and historical use

Although no studies were included, 13 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of disulfiram.

In 1949, oral disulfiram was approved for treating alcohol use disorder (AUD).[18] Disulfiram works by inhibiting aldehyde dehydrogenase, which metabolizes a toxic metabolite of alcohol, acetaldehyde.[18] This inhibition causes an increase in the acetaldehyde concentration, producing a disulfiram-ethanol reaction which includes nausea, vomiting, flushing, sweating, hypotension, palpitations, and on rare occasions, serious reactions such as cardiovascular collapse.[18] Disulfiram's presumed effectiveness is based on the patient's fear of the adverse effects and not a direct pharmacologic action.[18]

In the latest American Psychiatric Association guideline for AUD, released in 2018, injectable disulfiram is not mentioned. The guideline stated that oral disulfiram may be offered to patients with moderate to severe AUD under certain conditions.[19] These conditions include having a goal of achieving abstinence, preferring disulfiram or not responding to naltrexone and acamprosate, being capable of understanding the risks of alcohol consumption while taking disulfiram, and having no contraindications to disulfiram.[19]

One study by Carey-Smith et al specifically mentioned intramuscular administration of disulfiram. In this study, there were 3 groups with 5 patients each.[20] Group A was given 1 g of disulfiram in soybean emulsion via intramuscular injection.[20] Group B was given oral disulfiram and group C served as the control group given no medication or placebo.[20] Patients given the injection reported feeling weak and tired for 1-2 days, and some described feeling faint, dry mouth, headache, and influenza-like symptoms over the same time period.[20] Two patients had more severe systemic reactions, which included flushing, nausea, anorexia, and dizziness.[20] Carey-Smith et al reported that despite the initial side effects, the patients found the injection to be an acceptable alternative therapy.[20] However, they concluded that the "high incidence and severity of side effects preclude further clinical use of disulfiram in this form."[20]

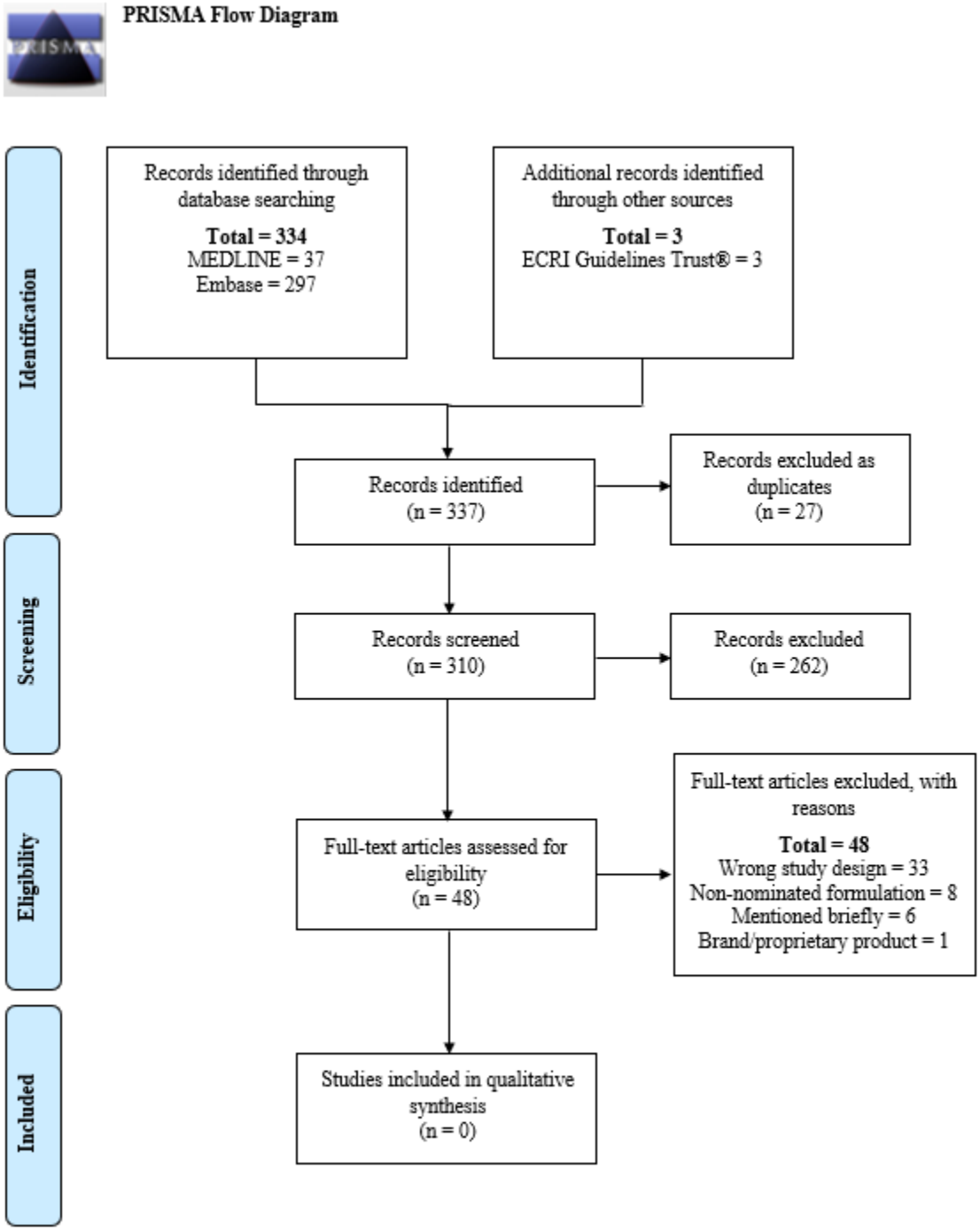
No further studies regarding the nominated formulation of an intramuscular injection were found. However, there have been studies and reviews about disulfiram implants, usually administered subcutaneously, with one study[15] in which the implants were administered intramuscularly. Disulfiram implants have been used since the 1950s.[13,21] The first use of subcutaneous disulfiram implants was described in a 1968 case report.[15-17] In many of the earlier reports, disulfiram implants were "largely ineffective due to their failure to release adequate levels of disulfiram, [and] risks of surgical complications such as infection and reject."[13] In a 1996 literature review by Hughes and Cook, 14 studies describing the use of disulfiram implants were identified.[11] Most of the early studies had poor methodologies, such as not having control groups or control groups without placebo implants.[11] Most of these earlier studies used 1 g of disulfiram implanted as 10 tablets in the lower abdominal wall.[11] A series of disulfiram implant studies were done by Wilson et al.[22-25] In these studies, Wilson et al compared the effectiveness of disulfiram implants to that of placebo implants or "sham" operations.[23-25] In one of the studies, disulfiram implants did not have an advantage over the placebo.[25] Both groups were able to achieve a longer abstinence period after treatment, demonstrating that disulfiram is a psychological deterrent since patients in the placebo group probably abstained from drinking for fear of adverse effects.[16,25] The other 2 studies by Wilson et al[23,24], showed that the disulfiram implants produced a "significant increase in days of abstinence or a significantly longer abstinence duration" compared to the placebo group.[16] More than half of the patients who drank alcohol in the disulfiram implant group experienced disulfiram-ethanol reactions,

pointing to “the pharmacological effects of disulfiram [increasing] the abstinent duration or days of abstinence.[16] The last study done by Wilson et al[22] used different disulfiram implant doses and found no significant differences among the doses, concluding that “psychological deterrence might outweigh pharmacological deterrent effects.”[11,22] However, these Wilson et al studies had methodological problems such as data loss during the follow-up period, a lack of details for patient matching to particular treatments, and reliance on self-reports.[11,16]

More recent double-blinded randomized controlled studies in disulfiram implants “have only been able to demonstrate a psychological effect.”[11] In a placebo-controlled study done by Johnsen and Morland, patients were randomized to receive 10 disulfiram 100 mg tablets for subcutaneous abdominal implant compared to that of the placebo group.[21] The placebo group received 9 calcium phosphate 100 mg tablets with 1 calcium phosphate tablet containing 1 mg of disulfiram.[21] The study concluded that there were no significant differences between the 2 groups for “reduction in average alcohol consumption, number of days to the first alcohol intake after implantation, or level of psychosocial function.”[21] The disulfiram group did have a significantly higher incidence of wound complications.[21] Hughes and Cook pointed out in their review that the lack of disulfiram implant efficacy in the trials could be due to the “insignificant absorption of disulfiram implant or inadequate amount of disulfiram being released” compared to that of the daily oral dose.[11,16] It was estimated, assuming no problems of poor absorption and tendency of disulfiram to aggregate, a 1 g implant that lasts 6 months only released about 5.6 mg/day compared to a daily oral dose of 200 mg.[11]

One study retrospectively analyzed the medical records of 32 intramuscular implantation procedures done at the authors’ clinic.[15] For the procedure, 10 100 mg disulfiram tablets were implanted either subcutaneously (7 patients) or intramuscularly (25 patients).[15] Subcutaneous implants were only done in the first 2 years of the study due to high complication rates, leading the study authors to prefer the intramuscular implantation method.[15] The authors concluded that wound complications can be overcome by “implantation in the subscapular intramuscular plane [which] allows [for] both uneventful healing and an out-of-reach implant location.”[15]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No studies included

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Three SMEs discussed disulfiram. Amongst these 3 SMEs, there were 2 medical doctors and 1 pharmacist. The SMEs specialized and/or were board-certified in child and adolescent psychiatry and psychiatry, working in academia and academic medical centers. The SMEs had been in practice for 10 to 30 years.

Disulfiram has fallen out of favor because it is difficult to study and when compared to placebo, disulfiram does not always look better. This could be due to the patients' belief that they will have a reaction if they drink, so even patients in the placebo arm will likely avoid drinking, therefore they will probably do as well as the patients on disulfiram. Patients on disulfiram also have variable reactions if they continue to drink; some will have minimal reactions while others have a strong reaction. An SME commented that there are some practitioners who put everyone on disulfiram; however, for this SME, disulfiram is not first line and they prefer to minimize its use. Instead they limit disulfiram to patients who want to take it, who are highly motivated to stop drinking, and who have a stable house and family situation. It is important to know which patients to give disulfiram to because there can be a high success rate in select patients and this SME has had patients who have been on disulfiram for years. If adherence is an issue or concern, disulfiram would not be a good option and the SME would choose a different medication. There are other medications available that are available as a dept injection, most of which will reduce cravings and make the patient drink less. Another SME stated there are challenges with taking disulfiram and that "[it is] kind of scary." One SME also commented that disulfiram tablets have been on short supply, so disulfiram has been used less lately.

The SMEs had not seen disulfiram used as an injection. One SME was interested in disulfiram as an implant many years ago because of adherence issues. A potential reason for intramuscular use could be due to the growing interest for use in certain types of cancers. For a depot preparation, one SME expressed they would be worry about the safety since it would be in the system for a long time. Another SME mentioned that a depot preparation does not make sense because disulfiram irreversibly blocks aldehyde dehydrogenase, and it takes several weeks to get over this blockade.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which disulfiram prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded disulfiram

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded disulfiram

No respondents to survey distributed via professional medical associations

CONCLUSION

Disulfiram was nominated for inclusion on the 503B Bulks List for treatment of alcohol addiction via a 250 mg/mL intramuscular injection solution in a single dose vial. Disulfiram is not available in the nominated dosage form and ROA in the US or any of the national medical registries searched.

Although no studies were included for the literature review, from the studies identified for the pharmacology section, disulfiram is used for alcohol addiction by inhibiting aldehyde dehydrogenase and causes a disulfiram-ethanol reaction. This reaction can cause nausea, vomiting, flushing, sweating, hypotension, palpitations, and on rare occasions, serious reactions such as cardiovascular collapse.[18] In the American Psychiatric Association guidelines for AUD, oral disulfiram may be offered to patients with moderate to severe AUD under certain conditions. One study mentioned use of intramuscular disulfiram but concluded that the "high incidence and severity of side effects preclude further clinical use of disulfiram in this form."[20] Other studies found evaluated the use of disulfiram implants, typically administered subcutaneously.

From the interviews conducted, disulfiram has fallen out of favor because it is hard to study and does not always produce better results when compared to placebo. One SME limits disulfiram to patients who want to take it, are highly motivated to stop drinking, and have a stable house and family situation. None of the SMEs had seen disulfiram used as an injection. One SME was interested in a disulfiram implant years ago because of adherence issues and another stated that the interest in intramuscular use could be due to the growing interest for use in certain types of cancers. For the depot preparation, one SME was worried about how long it would be in the system while another SME expressed this preparation would not make sense because it takes several weeks to reverse the aldehyde dehydrogenase blockade.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 6, 2020
- Date last searched: March 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 37

1	disulfiram/	200
2	disulfi#am$.tw.	453
3	disulphiram$.tw.	1
4	or/1-3	468
5	injections/	3371
6	exp injections, intravenous/	2181
7	injections, intramuscular/	2100
8	injections, subcutaneous/	2625
9	inject$.tw.	148662
10	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	1967
11	intravenous$.tw.	58118
12	intra venous$.tw.	156
13	intravascular$.tw.	8281
14	intra vascular$.tw.	69
15	intramuscular$.tw.	9960
16	intra muscular$.tw.	173
17	subcutaneous$.tw.	35950
18	or/5-17	235449
19	drug therapy/	1477
20	alcoholism/	4854

21	exp neoplasms/	450622
22	exp antineoplastic protocols/	21290
23	de.fs.	360133
24	dt.fs.	322616
25	ad.fs.	189799
26	tu.fs.	269260
27	therap$.tw.	787431
28	treat$.tw.	1475682
29	alcohol$.tw.	88958
30	cancer$.tw.	561091
31	anticancer$.tw.	36044
32	neoplas$.tw.	53940
33	antineoplas$.tw.	3572
34	tumo?r$.tw.	429302
35	antitumo?r$.tw.	27857
36	or/19-35	2549322
37	and/4,18,36	47
38	exp animals/ not humans/	435555
39	37 not 38	37
40	limit 39 to english language	37

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 9, 2020
- Limits: Humans (search hedge); English language
- Number of results: 297

1	disulfiram'/de	9365
2	disulfiram*':ti,ab,tn	3968
3	disulfizam*':ti,ab,tn	0
4	disulphiram*':ti,ab,tn	44
5	#1 OR #2 OR #3 OR #4	9771
6	intramuscular drug administration'/de	71558
7	intravascular drug administration'/de	317
8	intravenous drug administration'/exp	391902
9	subcutaneous drug administration'/de	100774
10	injection'/exp	247453
11	inject*':ti,ab	1082000
12	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18105
13	subcutaneous*':ti,ab	245757
14	intravenous*':ti,ab	482508
15	intra venous*':ti,ab	1434
16	intravascular*':ti,ab	67454
17	intra vascular*':ti,ab	675
18	intramuscular*':ti,ab	74342
19	intra muscular*':ti,ab	1269
20	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	2040348
21	drug therapy'/de	711199
22	add on therapy'/de	18515

23	adjuvant therapy'/exp	156678
24	neoplasm'/exp	5033778
25	alcoholism'/de	135229
26	alcohol abuse'/exp	38655
27	alcoholism therapy'/de	598
28	drug dose':lnk	621819
29	drug administration':lnk	1718631
30	drug therapy':lnk	3843836
31	therap*':ti,ab	4074510
32	treat*':ti,ab	7768530
33	cancer*':ti,ab	2496182
34	anticancer*':ti,ab	157516
35	neoplas*':ti,ab	368143
36	antineoplas*':ti,ab	26629
37	tumo$r*':ti,ab	2346056
38	antitumo$r*':ti,ab	192229
39	alcohol*':ti,ab	470742
40	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	14999317
41	#5 AND #20 AND #40	630
42	[animals]/lim NOT [humans]/lim	6001338
43	#41 NOT #42	390
44	#41 NOT #42 AND [english]/lim	297

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded disulfiram. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer disulfiram to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer disulfiram by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Intramuscular injection
   - o None of the above

4. I prescribe or administer disulfiram for the following conditions or diseases: (check all that apply)

   - o Alcohol addiction
   - o Other (please explain) _____

5. I use compounded disulfiram because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing disulfiram.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded disulfiram at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded disulfiram from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.