EBioMedicine 26 (2017) 132–137

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

# MSBIS: A Multi-Step Biomedical Informatics Screening Approach for Identifying Medications that Mitigate the Risks of Metoclopramide-Induced Tardive Dyskinesia

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ARTICLE INFO

*Article history:*
Received 16 October 2017
Received in revised form 7 November 2017
Accepted 20 November 2017
Available online 22 November 2017

*Keywords:*
Tardive dyskinesia
Metoclopramide
Drug safety
Drug-drug interactions
Drug repurposing
Combination therapy

ABSTRACT

In 2009 the U.S. Food and Drug Administration (FDA) placed a black box warning on metoclopramide (MCP) due to the increased risks and prevalence of tardive dyskinesia (TD). In this study, we developed a multi-step biomedical informatics screening (MSBIS) approach leveraging publicly available bioactivity and drug safety data to identify concomitant drugs that mitigate the risks of MCP-induced TD. MSBIS includes (1) TargetSearch (http://dxulab.org/software) bioinformatics scoring for drug anticholinergic activity using CHEMBL bioactivity data; (2) unadjusted odds ratio (UOR) scoring for indications of TD-mitigating effects using the FDA Adverse Event Reporting System (FAERS); (3) adjusted odds ratio (AOR) re-scoring by removing the effect of cofounding factors (age, gender, reporting year); (4) logistic regression (LR) coefficient scoring for confirming the best TD-mitigating drug candidates. Drugs with increasing TD protective potential and statistical significance were obtained at each screening step. Fentanyl is identified as the most promising drug against MCP-induced TD (coefficient: −2.68; p-value < 0.01). The discovery is supported by clinical reports that patients fully recovered from MCP-induced TD after fentanyl-induced general anesthesia. Loperamide is identified as a potent mitigating drug against a broader range of drug-induced movement disorders through pharmacokinetic modifications. Using drug-induced TD as an example, we demonstrated that MSBIS is an efficient in silico tool for unknown drug-drug interaction detection, drug repurposing, and combination therapy design.



## 1. Introduction

Metoclopramide (MCP) is an antiemetic and gastrointestinal (GI) agent, and the only medication approved by the U.S. Food and Drug Administration (FDA) for the indication of gastroparesis. The mechanism of action is its dopamine (DA) receptor antagonistic activity which suppresses the effects of DA and promotes the release of acetylcholine (Ach) (Wijemanne et al., 2016). The increase of Ach level improves the symptoms of gastroparesis by speeding up stomach muscle movement and stomach emptying. Its antiemetic effect is the result of DA and serotonin (5-$HT_3$) receptor inhibition in the nausea and vomiting centers of the brainstem.

In 2009, the FDA placed a black box warning on the chronic use of MCP due to the increased risks and prevalence of tardive dyskinesia (TD). The term TD refers to the classic tardive dyskinesia (CTD), characterized by involuntary and repetitive movements of the extremities, lip smacking, grimacing, tongue protrusion, rapid eye movement or blinking, puckering and pursing of the lips, or impaired movement of the fingers. These symptoms are rarely reversible and there is no known treatment. Since the development of TD is related to the duration of the MCP therapy, the FDA recommends that patients not use MCP longer than three months.

Despite of the severe neurotoxicity, the pathophysiology of MCP-induced TD is still not fully understood. The causality has been hypothesized to be the DA-Ach imbalance resulting from blockade of DA receptors (Stahl et al., 1982). Studies have shown that MCP and other DA antagonists can cross the blood-brain barrier (BBB) and cause DA-Ach imbalance in the striatum (Rao and Camilleri, 2010; Massara et al., 1985; Jolliet et al., 2007). Elevated Ach levels have been observed in the striatal region of the brain in animal models (Bymaster et al., 1986; Damsma et al., 1990; Schulze-Delrieu, 1981). As a result, anticholinergic (AC) medications have been employed to correct the DA-Ach imbalance and have had some success in treating various types of

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https://doi.org/10.1016/j.ebiom.2017.11.015

drug-induced movement disorders, including akathisia and dystonia (Greene et al., 1988; Qiu and Lim, 2011; Wei et al., 2012; Waln and Jankovic, 2013). However, in the case of drug-induced CTD, symptoms may persist or even exacerbate after AC medication co-administration (Brotchie et al., 2011; Rana et al., 2013). The American Academy of Neurology (AAN) has drawn no conclusion on AC therapy for TD treatment (Khouzam, 2015; Bhidayasiri et al., 2013). In light of these conflicting reports, our hypothesis is that not all medications with AC activity have appropriate mitigating effects on MCP-induced TD, particularly on CTD. It depends on how well a medication modulates the drug-induced DA-Ach imbalance. If the imbalance continues due to either insufficient or excessive Ach antagonism exerted by the secondary medication, not only will the TD symptoms persist, but also they will likely deteriorate. Therefore, there is a need to develop a systematic and efficient approach to screen and identify concomitant medications that can restore the delicate DA-Ach balance, and mitigate or even prevent MCP-induced TD. Here we present a multi-step biomedical informatics drug screening approach (MSBIS) that leverages informatics on bioactivity and post-market drug safety data for rapid discovery of effective secondary medications in the context of mitigating drug-induced TD toxicity.

## 2. Materials and Methods

We have developed a multi-step informatics approach to screen and identify concomitant drugs for mitigating toxicity induced by the primary drug. The overall workflow of the approach is illustrated in Fig. 1. Each of the screening steps is described below.

### 2.1. Ach Modulating Activity Scoring

Anticholinergics are a class of drugs designed to provide therapeutic benefits in a variety of disease states through inhibiting muscarinic Ach receptors in the CNS and peripheral systems. However, many medications outside the anticholinergics drug class may also elicit AC pharmacologic responses through off-target interactions. 120 medications have been classified to possess AC activity by clinicians (Hester, 2011). In the first screening step, we considered all 120 medications that encompass traditional anticholinergics/antimuscarinics as well as a large number of medications that are not regarded as traditional anticholinergics/antimuscarinics.

Our approach leverages the ever-increasing wealth of publicly available bioactivity and drug safety data. ChEMBL (Gaulton et al., 2012), the largest bioactivity database in the world, contains >1.5 million small molecules, 10,000 receptors, and 14 million bioactivity records. We have developed TargetSearch, an in-house bioinformatics web service (http://dxulab.org/software) to mine the vast amount of ChEMBL pharmacological data for relevant drug-receptor interactions including off-target polypharmacy (Xu et al., 2017). Here we used TargetSearch to score the anticholinergicity of the 120 drugs. The molecular structures of the 120 drugs were retrieved from DrugBank (Knox et al., 2011) and used as TargetSearch queries. ChEMBL was searched for either known bioactivity between a medication and 5 muscarinic Ach receptor subtypes (M1 – M5) or unknown off-target interactions via inferred structure-bioactivity relationships. If a query medication was found to have similar structure and chemical features to a bioactive molecule in the ChEMBL database, and this bioactive molecule had known bioactivity data associated with any of M1 to M5 receptors, we could infer that the medication would share similar bioactivity on the same receptors. The widely used extended connectivity fingerprint (Morgan) algorithm (Yildirim et al., 2007) was employed in the bioinformatics screening. A 10 μM bioactivity cutoff was used to ensure a higher level of confidence in identifying known and inferred relationships. When a hit was found, the receptor-specific AC scores were calculated from the Tanimoto coefficients reported by TargetSearch (Willett, 2006), which represents the drug's Ach modulating activity. The receptor-specific AC scores are in a [0, 1] range. A receptor-specific AC score of 1 indicated a medication had known bioactivity to a muscarinic Ach receptor whereas a score of 0 meant no known or inferred interaction was found. A score between 0 and 1 indicated that an inferred interaction was identified. The individual receptor subtype AC scores were averaged to give the mean AC score of a medication. This computational approach, illustrated in Fig. 2, essentially accounts for the pharmacodynamic interactions of a drug with muscarinic Ach receptors. It is fast, systematic, and has been shown to effectively capture drug off-target polypharmacy (Keiser et al., 2009) and measure drug-induced AC toxicity burden (Xu et al., 2017).

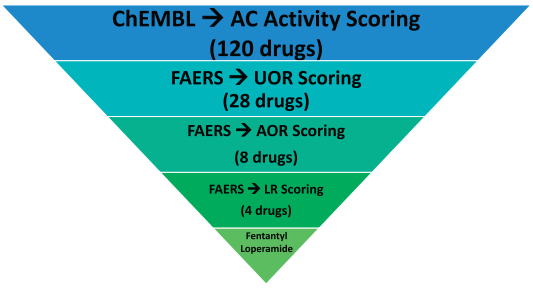


**Fig. 1.** The workflow of the MSBIS drug screening approach.

### 2.2. FDA Adverse Event Reporting System (FAERS)

An in-house FAERS relational database (January 2004 – June 2015) was used to detect and evaluate the drug-drug interactions between MCP and a secondary medication that lead to a decrease in MCP-induced TD incidences. FAERS is a public database for reporting adverse drug reactions (ADRs). It is one of the largest repository of ADR reports in the world, containing information voluntarily submitted by healthcare professionals, manufacturers, lawyers, and consumers in the United States (US) and other countries (Weiss-Smith et al., 2011). FAERS has been widely used in many post-marketing pharmacovigilance and drug safety research studies (Yue et al., 2014; Lorberbaum et al., 2016; Cortes et al., 2015; Kimura et al., 2015; Deepak et al., 2013; Oshima, 2011; Piccinni et al., 2011; Zhao et al., 2013).

To remove confounding by other TD-causing medications, an exclusion list of 26 TD-related drugs was compiled for this study. The drug exclusion list used in our FAERS queries is described in the Supplemental Materials.

### 2.3. Unadjusted Odds Ratio (UOR) Scoring

Based on data collected from FAERS, we calculated the UOR scores for each of the 28 selected drugs to assess the preliminary MCP-induced TD risk mitigating potential. The UOR (also known as reporting odds ratio) is a widely used method in adverse drug event signal detection (Rothman et al., 2004). It has been employed extensively in many published studies based on FAERS data (Zhao et al., 2013; Fujimoto et al., 2014; Hoffman et al., 2013; Yoshimura et al., 2013). A UOR (>1.0) indicates an increase of adverse drug events whereas a UOR (<1.0) signals a reduction of adverse drug events. Here we applied a much more stringent UOR cutoff (<0.09) to identify drugs with strong TD-mitigating indication.

The UOR score is defined as $\frac{a/b}{c/d}$, where *a, b, c,* and *d* are the number of safety reports under a background of MCP treatment, in which patients had undergone additional drug treatment ('Drug B') leading to a specified outcome: *a* is the number of safety reports in patients received drug B, such as a drug with AC activity, and had the TD adverse event; *b* is the number of safety reports in which patients received drug B and did not have the TD adverse event; *c* is the number of safety reports in which patients did not receive drug B and had the TD adverse event; and *d* is the number of safety reports in which patients did not receive drug B and did not have the TD adverse event (Table 1).

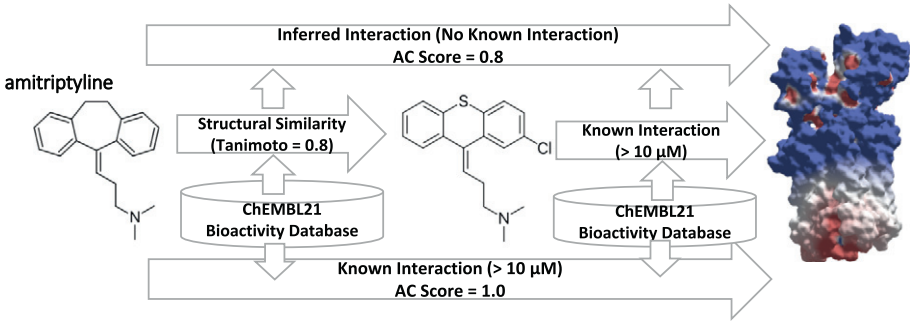


**Fig. 2.** Schematic workflow of TargetSearch AC scoring using amitriptyline as an example.

### *2.4. Adjusted Odds Ratio (AOR) Scoring*

It is known that TD outcomes are affected by age (elderly patients are more likely to have TD) and by gender difference (females are more likely to have TD than males) (Yassa and Jeste, 1992). It is also likely that the drug safety report frequency was influenced by the black box warning that FDA placed in 2009. Therefore, we need to account for these confounding factors in the AOR scoring.

The AOR scores were calculated from logistic regressions adjusted for age, gender, and reporting year. For each concomitant drug B, two logistic regression analyses were performed for MCP and MCP + drug B in SAS version 9.4 (SAS Institute, 2014), and the adjusted odd ratios were obtained, respectively. The final AOR score for each drug B was calculated from the ratio of AOR (MCP + drug B)/AOR (MCP).

### *2.5. Logistic Regression (LR) Scoring*

The binary clinical outcome of having or not having drug-induced TD (0 or 1) is well-suited for LR analysis. We set a drug B as a covariate in each LR analysis performed in SAS version 9.4 (SAS Institute, 2014). There was no parameter given in the LR analyses other than having concomitant MCP and whether to include the drug exclusion list or not. The calculated LR coefficient score and *p*-value for each drug were used to evaluate the MCP-induced TD mitigating potential and the associated statistical significance. The complete LR output is provided in Tables S4 and S5 in the Supplemental materials.

## 3. Results

After the bioinformatics screening of AC activity, 28 drugs were selected from the 120 drugs based on the criteria that: they are (1) representatives in relevant major drug classes; (2) commonly prescribed; (3) of a wide range in Ach modulating activity, assessed by mean AC scores. (Table 2).

A total number of 5,718,949 safety reports were examined in our FAERS database after the drug exclusion list was applied. (Table S1) We found 23,077 reported TD cases, 78.56% (18,129 reports) of which were associated with MCP, and 4948 cases (21.44%) were not. MCP was included in a total of 47,407 safety reports. Males and females represented 35.25% and 56.62% of the population in which gender of patients was reported. The mean age of the population was 55.22.

**Table 1**
UOR calculations table.

| Exposure | MCP | |
|---|---|---|
| | TD reported (cases) | No TD reported (controls) |
| + Drug B | a | b |
| − Drug B | c | d |

+ with, − without.

The 28 selected drugs were then subject to the UOR evaluation based on FAERS data. Those with UOR score higher than 0.09 were removed from further consideration. A UOR score lower than 1.0 indicates that a drug is associated with a reduced rate of MCP-induced TD incidences. Thus by setting the UOR score cutoff to 0.09, we increased the level of confidence for 8 retained drugs: alprazolam, amitriptyline, atropine, diazepam, diphenhydramine, fentanyl, loperamide, and ranitidine. (Table 3) Among the 8 drugs, alprazolam had the highest number of safety reports (73,330) whereas atropine had the lowest reporting rate (4817 reports).

However, after adjusting for reporting year, age, and gender, only 4 of the 8 drugs had AOR scores below the 1.0 cutoff. This observation underscores the impact of these confounding variables on determining a drug's true TD mitigating potential. The 4 remaining drugs were atropine (AOR = 0.46), diphenhydramine (AOR = 0.76), fentanyl (AOR =

**Table 2**
AC scores for the 28 medications selected from the bioinformatics screening.

| Medication | Drug class | Muscarinic Ach Receptors | | | | | Mean AC score |
|---|---|---|---|---|---|---|---|
| | | M1 | M2 | M3 | M4 | M5 | |
| Amitriptyline | Antidepressants | 1 | 1 | 1 | 1 | 1 | 1 |
| Imipramine | Antidepressants | 1 | 1 | 1 | 1 | 1 | 1 |
| Brompheniramine | Antihistamines | 0.75 | 0.43 | 0.43 | 0.75 | 0.75 | 0.62 |
| Carbinoxamine | Antihistamines | 0.65 | 0.65 | 0.65 | 0.65 | 0.65 | 0.65 |
| Chlorpheniramine | Antihistamines | 1 | 1 | 1 | 1 | 1 | 1 |
| Diphenhydramine | Antihistamines | 1 | 1 | 1 | 1 | 1 | 1 |
| Benztropine | Anti-Parkinson agents | 1 | 1 | 1 | 1 | 1 | 1 |
| Trihexyphenidyl | Anti-Parkinson agents | 1 | 1 | 1 | 1 | 1 | 1 |
| Chlorpromazine | Antipsychotics | 1 | 1 | 1 | 1 | 1 | 1 |
| Haloperidol | Antipsychotics | 1 | 0.39 | 0.39 | 1 | 1 | 0.76 |
| Perphenazine | Antipsychotics | 0.78 | 0.78 | 0.78 | 0.78 | 0.78 | 0.78 |
| Risperidone | Antipsychotics | 1 | 1 | 1 | 1 | 1 | 1 |
| Thioridazine | Antipsychotics | 1 | 1 | 1 | 1 | 1 | 1 |
| Trifluoperazine | Antipsychotics | 0.81 | 0.7 | 0.81 | 0.81 | 0.70 | 0.77 |
| Alprazolam | Benzodiazepines | 0 | 0 | 0 | 0.30 | 0.30 | 0.12 |
| Clorazepate | Benzodiazepines | 0.34 | 0.34 | 0.34 | 0.34 | 0.34 | 0.34 |
| Diazepam | Benzodiazepines | 0.40 | 0.40 | 0.40 | 0.40 | 0.40 | 0.40 |
| Atropine | Gastrointestinal agents | 1 | 1 | 1 | 1 | 1 | 1 |
| Dicyclomine | Gastrointestinal agents | 1 | 1 | 1 | 1 | 1 | 1 |
| Hyoscyamine | Gastrointestinal agents | 1 | 1 | 1 | 1 | 1 | 1 |
| Loperamide | Gastrointestinal agents | 0.49 | 0.49 | 0.49 | 0.49 | 0.49 | 0.49 |
| Promethazine | Gastrointestinal agents | 1 | 1 | 1 | 1 | 1 | 1 |
| Ranitidine | Gastrointestinal agents | 0.65 | 0.65 | 0 | 0 | 0 | 0.26 |
| Orphenadrine | Muscle relaxants | 1 | 1 | 1 | 1 | 1 | 1 |
| Fentanyl | Opioid Analgesic | 0.39 | 0.42 | 0.42 | 0.38 | 0.38 | 0.41 |
| Flavoxate | Anticholinergics | 0.34 | 1 | 1 | 0.33 | 0.34 | 0.60 |
| Oxybutynin | Anticholinergics | 1 | 1 | 1 | 0.52 | 0.46 | 0.80 |
| Tolterodine | Anticholinergics | 1 | 1 | 1 | 1 | 1 | 1 |

**Table 3**
Summary of the calculated TD incident rates, UOR and AOR scores.

| Drug B | MCP | | UOR | 95% CI | p-Value | AOR[a] |
|---|---|---|---|---|---|---|
| | TD% (+ Drug B) | TD% (− Drug B) | | | | |
| Alprazolam | 73/1251 (5.84%) | 17,797/41915 (42.46%) | 0.084 | (0.070–0.110) | 4.10E-92 | 4.34 |
| Amitriptyline | 40/1007 (3.97%) | 17,830/42159 (42.29%) | 0.056 | (0.040–0.080) | 8.65E-70 | 3.48 |
| Atropine | 4/241 (1.66%) | 17,866/42925 (41.62%) | 0.024 | (0.009–0.064) | 4.32E-13 | 0.46 |
| Diazepam | 33/972 (3.40%) | 17,837/42194 (42.27%) | 0.048 | (0.030–0.070) | 9.09E-65 | 1.64 |
| Diphenhydramine | 30/1058 (2.84%) | 17,840/42108 (42.37%) | 0.040 | (0.030–0.060) | 7.85E-67 | 0.76 |
| Fentanyl | 10/1685 (0.59%) | 17,860/41480 (43.06%) | 0.008 | (0.004–0.010) | 1.13E-51 | 0.07 |
| Loperamide | 5/1091 (0.46%) | 17,865/42075 (42.46%) | 0.006 | (0.003–0.020) | 5.73E-29 | 1.33E-05 |
| Ranitidine | 57/2081 (2.74%) | 17,830/42159 (42.29%) | 0.037 | (0.030–0.050) | 1.06E-131 | 1.30 |

[a] Adjusted for reporting year, age, and gender. + with; − without.

0.07), and loperamide (AOR = 1.33E-5). (Table 3) The raw UOR, AOR scores, and 95% CIs for all 8 drugs are listed in Table S2.

Since TD may also be used to describe multiple drug-induced extrapyramidal disorders including CTD, tardive akathisia, tardive dystonia, tardive tremor, etc. (Wijemanne et al., 2016; Waln and Jankovic, 2013), it is necessary to evaluate these related adverse events in our FAERS queries to account for generalized or inaccurate reporting. The UOR scores related to the overall movement-related adverse events (MedDRA terms: extrapyramidal disorder, movement disorder, dyskinesia, akathisia, dystonia, and tremor) are shown in Table S3 and Fig. S1. All 8 drugs had the UOR scores below 1.0. There were zero cases reported for atropine with akathisia and loperamide with movement disorder. Similar to the TD incidence rates reported in Table 3, Fig. 3 shows the remarkable differences of administrating MCP with and without "drug B" in the overall movement disorders.

Fig. 4 summarizes the LR coefficient scores calculated from the LR analyses for the 8 drugs with and without the drug exclusion list applied. Negative LR coefficient scores represent a protective or mitigating effect against MCP-induced TD. Our data showed that the same 4 drugs had negative LR coefficient scores: atropine (−0.712), diphenhydramine (−0.269), fentanyl (−2.682), and loperamide (−14.018), in good agreement with the AOR results listed in Table 3. However, among these 4 drugs, only fentanyl had statistically significant LR coefficient scores: −2.682 (p-value = 0.004 with the drug exclusion list applied), and −0.8043 (p-value = 0.006 without the drug exclusion list applied). Loperamide, on the other hand, had more favorable LR coefficient scores than fentanyl, but they are only statistically significant without the drug exclusion list applied, indicating that loperamide may have a broader mitigating effect against other TD-causing drugs. Our results also suggested that gender might play a role in the TD clinical outcome. Despite of the lack of statistical significance, negative LR coefficient scores were associated with men (protective effects) whereas positive LR coefficient scores were associated with women in all logistic regression output. (Tables S4 and S5).

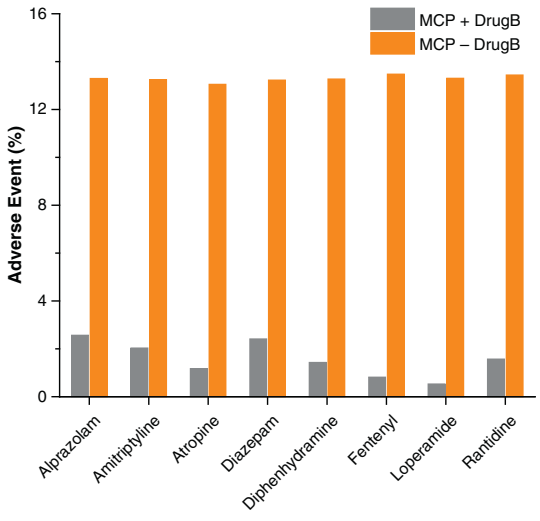


**Fig. 3.** The incidence rates of all reported adverse events potentially related to TD. (+ with; − without).

## 4. Discussion

### 4.1. Applying the MSBIS Approach in MCP-Induced TD Mitigation

The objective of this study is to apply and showcase our integrative biomedical informatics approach (MSBIS) that leverages big bioactivity and healthcare data to identify secondary medications for mitigating the adverse effects of a primary drug. (Fig. 1) In the context of mitigating MCP-induced TD, we showed that MCP is strongly associated with TD, accounting for 78.56% of all reported TD cases in FAERS. In Table 3, we showed that there is a high TD incidence rate (approximately 42%) in FAERS patients receiving MCP treatment, in good agreement with the analysis of 67 TD clinical case reports.(Sewell and Jeste, 1992) Based upon the DA-Ach imbalance theory, our first round of screening focused on drugs with varying degrees of Ach modulating activity, which was assessed by TargetSearch on 120 drugs. The first screening step yielded 28 commonly prescribed drugs, representing 9 major drug classes with a wide range of Ach modulation. In the second round of screening, we showed that 8 of the 28 drugs had a preliminary indication of TD-

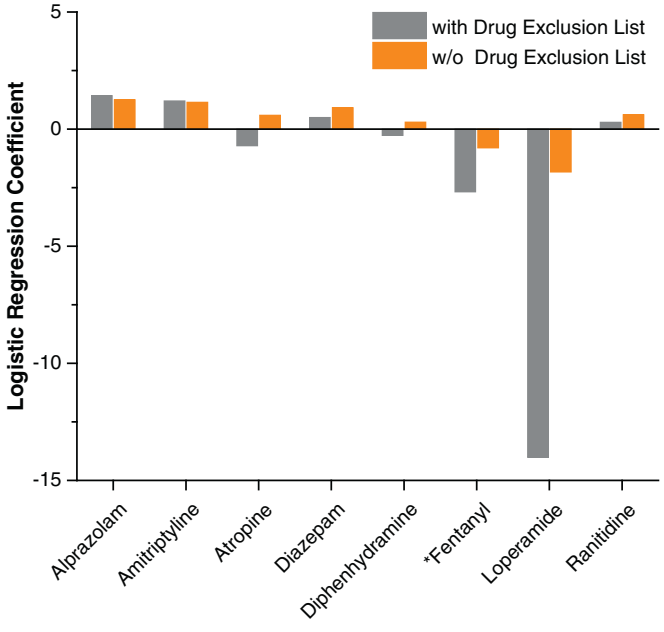


**Fig. 4.** A summary of drug MCP-induced TD mitigating effects measured by LR coefficient scores. *Fentanyl was the one drug having both p-values < 0.01 with and without the drug exclusion list applied. Loperamide has a p-value < 0.01 without the drug exclusion list applied.

mitigating effects represented by their UOR scores. The risks of developing TD and other TD-related movement disorders were significantly decreased with concomitant use of MCP and the 8 drugs. (Table 3, Fig. 2) Because reporting year, age, and gender are confounding variables to TD outcomes, the UOR results were further refined by the AOR analyses adjusted for these variables in the third screening step, leading to 4 drug candidates (atropine, diphenhydramine, fentanyl, and loperamide). In the last screening step, multivariate LR analyses were carried out for each of the 4 drugs as a covariate. We observed substantial TD-mitigating effects in fentanyl and loperamide whereas the effects in atropine and diphenhydramine were marginal. The relative magnitude of the observed mitigating effects (i.e. LR coefficient scores) was consistent with that of the AOR scores. The effectiveness of the MSBIS approach was evident that at each screening step we identified drugs with increasing TD-mitigating effects and statistical significance.

### 4.2. Mitigating a Broader Range of Drug-Induced TD

To investigate if any of the 8 drugs provide protective effects against all TD-causing drugs, we removed the drug exclusion list and re-ran the LR analyses. Fig. 3 shows that the 4 drugs that did not show protective effects against MCP-induced TD did not protect patients from other TD-causing drugs either. Although atropine and diphenhydramine had marginal protective effects against MCP-induced TD, they were not protective against other TD-causing drugs. Both fentanyl and loperamide showed substantial mitigating effects against all TD-causing drugs and the results were statistically significant.

### 4.3. Fentanyl

Fentanyl was the only drug that showed statistically significant TD-mitigating effects against both MCP-induced TD and TD induced by other medications. These results confirmed our discovery of fentanyl as the most promising drug candidate to prevent or mitigate a broad range of drug-induced TD adverse events. Indeed, there has been a reported case that a 44 year old woman with a severe drug-induced TD completely recovered after fentanyl-induced general anesthesia in a minor orthopedic operation (Johnsen and Wester, 2002). Her full remission of TD symptoms had remarkably lasted for 41 months at the time of case report. The clinicians believed that fentanyl used to induce the general anesthesia caused a permanent change in the neuronal circuitry involved in her TD (Johnsen and Wester, 2002).

### 4.4. Loperamide

Loperamide showed a much greater TD-mitigating potential than fentanyl against TD induced by MCP as well as other medications. The LR coefficient scores and p-values implied that loperamide may be protective against a broader range of TD-causing drugs. Its mechanisms of action, however, would be quite different from fentanyl because loperamide cannot effectively penetrate the BBB (Upton, 2007). Loperamide inhibits muscarinic Ach receptors in the gastrointestinal (GI) tracts, and slows the GI mobility induced by MCP. Studies have shown that loperamide modifies the pharmacokinetics of orally co-administered drugs (Knupp et al., 1993). The adsorption rate and plasma level ($C_{max}$ and AUC) of a co-administered drug are substantially decreased by loperamide (Knupp et al., 1993; Goineau et al., 2015). In contrast, MCP has been shown to increase the absorption and plasma concentration of concomitant drugs, leading to higher risks of drug-induced toxicity (Prescott et al., 2004). Therefore, the competing pharmacology of loperamide and MCP not only contributes to the protective effect against MCP-induced toxicity (including TD), but also explains why loperamide may be effective to reduce the risks of other TD-causing agents. The other factor is drug metabolism. MCP is primarily metabolized by CYP2D6 (Rao and Camilleri, 2010). Although loperamide is primarily metabolized by CYP3A4 and CYP2C8, it had the highest affinity with CYP2D6 in the *N*-demethylation process (Kim et al., 2004). In another word, loperamide is a competitive inhibitor to MCP metabolism at CYP2D6.

### 4.5. Ach Modulating Activity and TD Mitigation

Many drugs in our initial screening had strong Ach modulating activity (AC scores > 0.6), which may not be appropriate for re-balancing the DA-Ach levels due to over-suppression. This may explain the clinical observations that anticholinergics and drugs with strong AC activity may persist or even exacerbate drug-induced TD (Bhidayasiri et al., 2013; Lerner et al., 2015). On the other hand, drugs with low AC activity (AC scores < 0.3) may be inadequate. The 2 best drug candidates (fentanyl and loperamide) had moderate AC activity (AC score = 0.41, 0.49, respectively). Diazepam is another drug having moderate AC activity (AC score = 0.40). However, the effect of diazepam on MCP-induced TD remains inconclusive, as indicated in our UOR and AOR analyses. There was some evidence that diazepam improves TD symptoms (Singh et al., 1983). Other case reports however have shown that diazepam did not relieve MCP-specific TD symptoms (Jankovic and Glass, 1985). Diazepam is also a GABAnergic agent. Due to the complex dynamics between DA, Ach, and GABA, it is difficult to access the net impact of diazepam on the MCP-induced DA-Ach imbalance. To summarize, our data suggested that having a moderate Ach modulating activity (AC score 0.4–0.5) is an important factor for a medication to restore the delicate DA-Ach balance in the CNS and produce a positive outcome in mitigating MCP-induced TD.

### 4.6. Gender Differences

Results from our LR analyses suggested gender plays a role in TD outcomes: males are generally less susceptible to drug-induced TD toxicity than females. (Tables S4 and S5) Despite that there were more females (56.62%) than males (35.25%) in the FAERS data, our finding is consistent with an analysis of 76 clinical cases, which showed a higher TD prevalence in women than men (Yassa and Jeste, 1992).

### 4.7. Limitations

Underreporting and misreporting of TD in FAERS are a potential limitation. To address this issue, we examined additional TD and movement disorder-related terms in the study. Because of the crowd sourcing data collection model used by FAERS, missing or incomplete data, reporting bias, and lack of information on individual patients (e.g., social and family history, occupation and education, etc.) inevitably exist. There may be other possible confounding factors, for example, the genetic predisposition of patients at a higher risk of TD. FAERS database does not provide any information regarding medication prescriptions nor the duration of therapy. The impact of these limitations is difficult to estimate because of the nature of FAERS data. Nevertheless, FAERS is a rich and invaluable post-market data resource for drug safety research.

### 4.8. Conclusions

We have demonstrated the potential and feasibility of the MSBIS approach in the search of medications that mitigate drug-induced TD. Fentanyl and loperamide were discovered in this study as promising TD-mitigating drugs with remarkably different mechanisms of pharmacological action. Our results illustrated that the MSBIS approach could be easily generalized to rapidly detect unknown drug-drug interactions, facilitate drug repurposing, and screen for drug combinations that either mitigate undesirable toxicity or synergize therapeutic effects. Follow-up studies are underway to further develop the MSBIS approach and validate the study findings using longitudinal medical claims data.

## Funding Sources

This work is, in part, supported by a sub-award of the Institutional Development Awards (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health (Grants numbers P20GM103408 and P20GM109095) to D.X., Idaho State University Faculty Seed Grant to D.X., Idaho State University Career Path Intern (CPI) Funding to A.G.M., S.T.F., P.J.E., H.K.D., and R.W.J., and Idaho State University College of Pharmacy Graduate Assistantship to A.T. None of the funders had any role in study design, data collection, data analysis, interpretation, or writing of the report.

## Conflict of Interest Statement

The authors declare no conflict of interest.

## Author Contributions

D.X. designed and lead the study; A.G.M., R.D.T, M.L.C, A.T., P.J.E., H.K.D., and R.W.J. performed the experiments and analyzed the data; S.T.F. and V.L.C. contributed to manuscript writing and revision.

## Acknowledgements

The authors thank Idaho State University Office of Research, Idaho State University College of Pharmacy, and Idaho State University Career Path Intern program for providing the research support. None of the funders had any role in study design, data collection, data analysis, interpretation, or writing of the report.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2017.11.015.

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