Applying IBM Watson cognitive computing to identify drugs with potential for treating L-DOPA-induced dyskinesia

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Background

Current treatment options for L-DOPA-induced dyskinesia (LID) are limited. Repurposing compounds with regulatory approval is an attractive approach to accelerate availability of novel therapeutic options. IBM Watson for Drug Discovery (WDD) is a cognitive computing platform that extracts domain specific text features from vast quantities of published literature to identify existing and infer novel connections between entities of interest, including drugs.

Objectives

To use WDD to analyze published abstracts of a set of compounds known to prevent LID and apply machine learning to rank a candidate set of compounds according to similarity of linguistic context and thereby discover compounds with potential for treating LID.

Methods

15 compounds, of a range of classes, with demonstrated ability to reduce LID pre-clinically or in clinical trials were identified as known compounds.

Class of compound	Compound name
NMDA receptor antagonists	
Cannabinoid receptor 1/2 partial agonist	
mGlu5 NAMs	
AMPA antagonists	
alpha2 adrenergic antagonists	
5-HT1A agonists	
5-HT1B agonists	
alpha 7 containing nicotinic agonists	
alpha 4 beta 2 containing nicotinic agonists	
mu/k-opioid receptor antagonist	

Table 1. Known compounds

Candidate compounds were filtered from the entire DrugBank database of 8261 entries including 2021 FDA-approved small molecule drugs, 233 FDA-approved protein/peptide drugs, 94 nutraceuticals and over 6000 experimental compounds (https://www.drugbank.ca/). Dopamine agonists and compounds with <5 published abstracts were removed, leaving 3539 final candidates. WDD analyzed ~1.3 million Medline abstracts and then, using machine learning, created a predictive model to rank candidate compounds based on semantic similarity to the known set (Figure 1).

Figure 1. Predictive analytics methodology

Each compound is converted to a vector, or "semantic fingerprint," representing the weighted frequency of the words and phrases in all abstracts that mention it. From these vectors, a distance matrix relating every compound in the known and candidate lists is generated. A semi-supervised learning approach, graph diffusion (1), is then used to rank candidate compounds by similarity to the overall 15 known compounds.

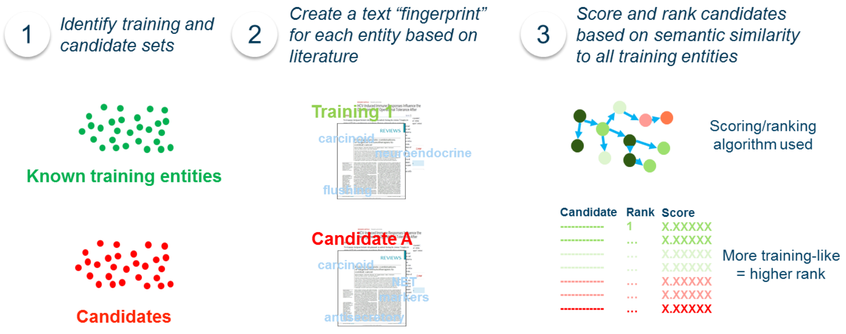


Figure 2. Leave-one-out cross-validation

The analysis is run 15 times, each time with one entity from the known set excluded and added to the candidate set. Wilcoxon p-value ($4.5x10^{-11}$) and area under the Receive-Operator Characteristics curve (AUC=0.72) demonstrate that the semantic models Watson has created from the known drugs have predictive power over each other compared to the candidate set.

Compound	Score	Rank/3554
	0.00528	1
	0.00528	2
	0.00528	3
	0.00522	4
	0.00520	5
	0.00517	6
	0.00507	7
	0.00475	9
	0.00475	10
	0.00462	11
	0.00317	24
	0.00163	94
	0.00004	610
	0.00003	642
	0.00001	940

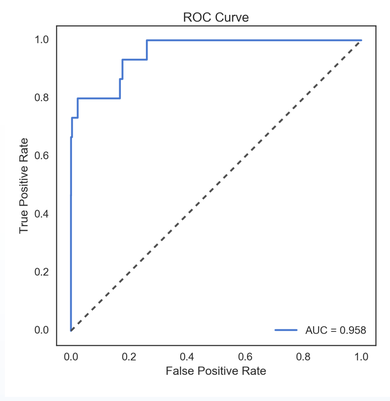


Table 2. Ranking of known compounds

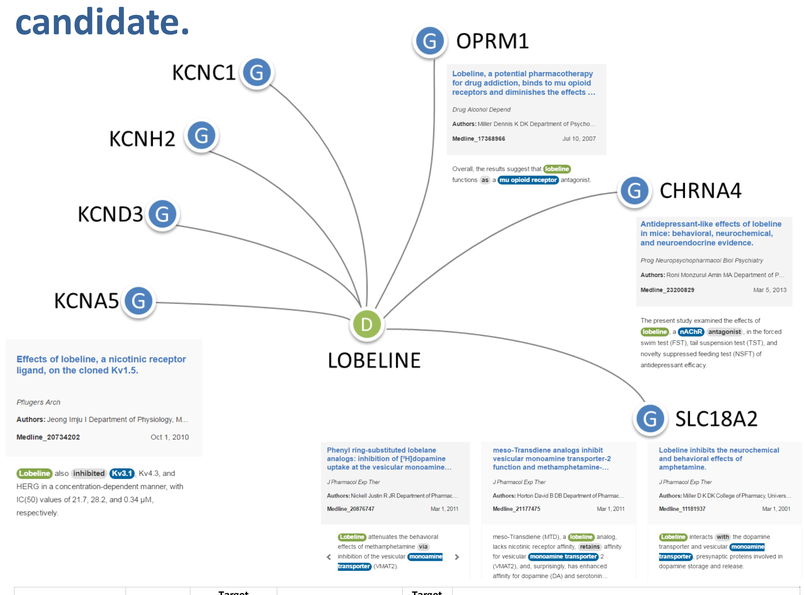
Retrospective analysis

To further validate WDD's methodology, the analysis was first restricted to abstracts published up to and including 2013. 3 known drugs with abstracts first demonstrating their antidyskinetic effects published after 2013 were omitted from the known set. Using only 7 and 4 available abstracts respectively, WDD ranked 2 of these highly, 111th, and 194th (top 5.5%) out of 3527 drugs. The third, ranked 857th (top 25%).

Prospective Analysis: Results

The top 50 ranked candidates were explored in WDD to determine their relationship with each drug in the known set, and reveal the biological connections that may contribute to their predicted antidyskinetic actions.

Figure 3. Case study of a highly ranked candidate.



Relationship type	Verb	Target (Canonical)	Target (Text)	Target type	Sentence fragment
Prepositional	as	OPRM1	mu opioid receptor	GENE	Overall, the results suggest that lobeline functions as a mu opioid receptor antagonist.
RegulationNegative	antagonist	CHRNA4	nAChR	GENE	The present study examined the effects of lobeline, a nAChR antagonist, in the forced swim test (FST), tail suspension test (TST), and novelty
Prepositional	with	SLC18A2	monoamine transporter	GENE	Lobeline interacts with the dopamine transporter and vesicular monoamine transporter, presynaptic proteins involved in dopamine
Prepositional	via	SLC18A2	VMAT2	GENE	Lobeline attenuates the behavioral effects of methamphetamine via inhibition of the vesicular monoamine transporter (VMAT2).
RegulationNegative/ Association	inhibited	KCNH2	HERG, KCNC1, Kv3.1, Kv4.3, Kv1.5	GENE	Lobeline also inhibited Kv3.1, Kv4.3, and HERG in a concentration-dependent manner,
RegulationNegative	attenuated	nicotine-induced hyperactivity	nicotine-induced hyperactivity	NA	Lobeline attenuated nicotine-induced hyperactivity when both drugs were administered repeatedly.
RegulationNegative	inhibit	blood-brain (bbb) transporter	the blood-brain barrier BBB amine transporter	NA	Lobeline is a potential smoking cessation drug with affinity for the α4β2 nicotinic acetylcholine receptor and may inhibit the blood-brain barrier (BBB) amine transporter.
Regulation	mediate	lobeline	the agonist effects of lobeline	NA	Although the alpha4beta2 receptor is unlikely to mediate the agonist effects of lobeline, our results indicate that lobeline does interact with the nicotinic receptor in a novel fashion.
Association	desensitize	(inhibition	receptors when applied alone inhibition	NA	Thus, lobeline can apparently desensitize receptors when applied alone (inhibition) whereas its binding to a second agonist site with the first one already occupied by acetylcholine leads to channel opening (potentiation).
RegulationNegative	reduces	epileptic seizures	epileptic seizures	NA	Hence, we may propose that lobeline reduces epileptic seizures by enhancing the GABA release supporting the GABAergic mechanism.
RegulationNegative	reduced	lobeline	the effects of lobeline	NA	The depressant effects of lobeline on the visual response could not be reversed by the GABA(A) antagonist bicuculline, but the GABA(B) antagonist CGP 35348 reduced the effects of lobeline.
RegulationNegative	decreased	locomotor	locomotor activity and body temperature in mice	NA	Lobeline, at the time of maximal effect, dose-dependently produced motor impairment and decreased locomotor activity and body temperature in mice after s.c.
Association	produced	hypoactivity	hypoactivity	NA	Lobeline produced hypoactivity in total horizontal activity and center distance travelled.
RegulationPositive	induced	stereotyped behaviors	any stereotyped behaviors	NA	In saline challenge groups, the doses of lobeline examined did not affect spontaneous locomotion nor induced any stereotyped behaviors.
RegulationNegative	attenuates	behavioral methamphetamine	the behavioral effects of methamphetamine	NA	Lobeline attenuates the behavioral effects of methamphetamine via inhibition of the vesicular monoamine transporter (VMAT2).
RegulationPositive	augments	cocaine-induced hyperactivity	cocaine-induced hyperactivity in rats	NA	Lobeline augments and inhibits cocaine-induced hyperactivity in rats.
Regulation	alters	presynaptic dopamine	presynaptic dopamine storage and release in brain	NA	Lobeline has high affinity for nicotinic receptors and alters presynaptic dopamine storage and release in brain.
Regulation	alters	dopamine	dopamine function	NA	Reevaluation of the mechanism by which lobeline alters dopamine function reveals that its primary mechanism is inhibition of dopamine uptake and promotion of dopamine release from the storage vesicles within the presynaptic terminal, via an interaction with the tetrabenazine-binding site on the vesicular monoamine transporter (VMAT2).
RegulationNegative	inhibit	da uptake synaptic vesicles	DA uptake into synaptic vesicles	NA	These results suggest that lobeline specifically interacts with DTBZ sites on VMAT2 to inhibit DA uptake into synaptic vesicles.
Localization	displaced	3h]cytisine cortical	3H]cytisine binding to rat cortical membranes	NA	Lobeline displaced [3H]cytisine binding to rat cortical membranes with a mean inhibition constant (KI) value of 16.0 nM, while the lobeline analogs CRM-I-13-1 and CRM-I-32-1 exhibited values of 15.0 and 5.4 microM, respectively.
Regulation	mediated	lobeline	the effect of lobeline	NA	While DMPP-induced 5-HT release can be linked to a non-classical nAChR activation ([Ca2+]o-independence), the effect of lobeline was likely mediated by uptake carriers.
RegulationNegative	attenuates	behavior deficits	behavior deficits in animals	NA	Lobeline shows protective effects against MPTP-induced dopaminergic neuron death and attenuates behavior deficits in animals.

Screen shots from WDD illustrating a selection of the gene relationship network for Lobeline (ranked 39/3539) and a table of a selection of the unconstrained relationship network .

Discussion

We have demonstrated the feasibility of using WDD to rank compounds based on their predicted potential to reduce LID. Further studies will be required to validate these predictions in animal models of LID. As well as identifying compounds with known and plausible antidyskinetic mechanisms of action, future work will address the antidyskinetic potential of compounds identified by WDD with a novel/unknown mechanism of action and test the power of WDD to uncover novel strategies to tackle this debilitating condition.

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