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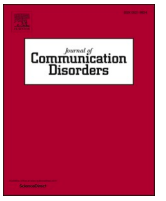

Characterizing drug-induced stuttering in electronic health records

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ABSTRACT

Purpose: Drug-induced stuttering is a phenomenon where the onset of stuttered speech is caused by exposure to pharmaceutical chemical substances. This acquired form of stuttering features many of the same overt speech behaviors as developmental stuttering. Investigations of drug-induced stuttering have been limited to adverse drug reaction reports and case studies. This study leveraged electronic health records (EHRs) at a major university medical center to identify drug-induced stuttering within medical notes, followed by classification of implicated drug types.
Methods: A previous systematic EHR review of approximately 3 million individuals to identify cases of developmental stuttering resulted in 40 suspected cases of drug-induced stuttering. In the present study, these cases were reviewed comprehensively to evaluate: name, class, and mechanism of action of suspected drug, level of evidence for the implicated drug as a causal agent, therapeutic measures taken, and progression or remission of stuttering.
Results: Eighteen different drugs were linked to possible drug-induced stuttering in 22 individuals. Antiseizure agents, CNS stimulants, and antidepressants were the most common drug classes implicated in drug-induced stuttering. topiramate (Topamax) was the most commonly implicated drug across all records reviewed.
Conclusions: This study represents the first analysis of health system data examining drugs implicated in drug-induced stuttering in a clinical setting. Augmenting previous case reports and database reviews, a variety of drugs were identified; however, improved reporting of drug-associated speech fluency changes within the EHR are needed to further amass evidence for suspected drugs and their associated epidemiological and clinical characteristics.

1. Introduction

Developmental stuttering is a neurodevelopmental speech condition characterized by repetitions of sounds, syllables, or words; prolongations of sound; and tension-filled pauses or breaks in speech known as blocks. Onset of the condition typically occurs in

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children between ages 2 and 5 (Yairi & Ambrose, 2013). Although less common, similar disruptions in speech fluency can occur beyond this developmental period. Collectively, various forms of non-developmental stuttering are called *acquired stuttering*. There are three subtypes of acquired stuttering: 1) *neurogenic stuttering*, or stuttering resulting from stroke, traumatic brain injury, and neurodegenerative disorders; 2) *functional* or *psychogenic stuttering*, or stuttering associated with acute psychological trauma, and 3) *drug-induced* or *pharmacogenic stuttering*, or stuttering stemming from drug side effects (Van Borsel, 2014). Developmental and acquired stuttering are largely indistinguishable based on symptomatology of verbal output alone (Jokel et al., 2007; Van Borsel & Taillieu, 2001). Neurogenic stuttering is the most common form of acquired stuttering and a growing body of literature has focused on characterizing neurogenic stuttering by the type and location of neurological damage and description of additional speech or language difficulties (Market et al., 1990; Theys et al., 2008, 2011; Van Borsel, 2014).

Much less is known about drug-induced stuttering with evidence largely based on case series, which are limited in size. Explanations for the lack of more systematic investigations of drug-induced stuttering include the relative rarity of the condition, the generally transient nature of the condition, and a lack of awareness of the condition by healthcare professionals. The latter may result in drug-induced stuttering misattributed to a worsening of a patient's psychiatric or neurological disorder rather than as an adverse reaction to a drug.

Although drug-induced stuttering is not widely recognized, a previous study found 724 individual case safety reports (ICSRs) in Vigibase, an international pharmacovigilance database maintained by the World Health Organization, suggesting that stuttering is not a rare or negligible adverse drug reaction (Trenque et al., 2021). A disproportionality analysis that estimated the association between exposure to a drug and the occurrence of stuttering within Vigibase found a variety of drugs reported to induce stuttering, including methylphenidate, topiramate (Topamax), and olanzapine (Zyprexa). Additionally, a recently published literature review of 63 drug-induced stuttering case reports and case series found 27 different drugs implicated in 82 cases (Nikvarz & Sabouri, 2022). The most commonly implicated classes of drugs were antipsychotics, central nervous system agents, and anticonvulsants; individual drugs associated with the most cases included pregabalin, methylphenidate, and adalimumab. Together, these studies suggest that drugs that affect neurotransmission are most likely to be implicated in drug-induced stuttering.

Incomplete and inconsistent reporting of drug-induced stuttering is a barrier for research on the phenomenon. While attempting to evaluate epidemiological and clinical characteristics of drug-induced stuttering via case reports, Nikvarz and Sabouri (2022) found inconsistent or poor reporting of a) stuttered speech characteristics (i.e., repetitions, prolongations, blocks), b) intervals between initiation of drug and onset of stuttering, c) therapeutic measures, such as drug removal or withdrawal, and d) improvement or progression of stuttering. The lack of pertinent details within case reports has led to an incomplete picture of drug-induced stuttering.

In addition to supporting document portability and facilitating billing, electronic health records (EHRs) can also be utilized for research and may provide a novel approach for investigating drug-induced stuttering using information collected during clinical encounters. Specifically, EHRs contain a variety of data sources including clinical notes, prescriptions, and procedural and billing codes, providing insight into how drug-induced stuttering is typically documented in medical settings and augmenting data from case reports. In the past decade, studies have demonstrated that clinical data from EHRs captured during routine healthcare services can produce data similar to prospective study collection (e.g., Byrne et al., 2013; Haerian et al., 2012; Karanevich et al., 2018; Newgard et al., 2012; Yin et al., 2022). Overall, expanding the scope of drug-induced stuttering research and increasing awareness of drug-induced stuttering may improve patient care while informing the pathogenesis of stuttering.

1.1. Study aims

Considering the current gaps in knowledge, our study aims to investigate drug-induced stuttering using EHRs within a major research university medical system to better characterize the condition at scale. This work focuses on a subset of novel instances of drug-induced stuttering that were initially identified, but not included, in a previous EHR-based study of developmental stuttering (Pruett et al., 2021). Specifically, suspected cases of drug-induced stuttering were reviewed by an expert in stuttering and a clinical pharmacist to: 1) describe the implicated drugs and therapeutic measures taken, 2) evaluate the level of evidence for the implicated drug as a causal agent, 3) characterize common reporting practices, and 4) discuss potential pathophysiological mechanisms.

2. Methods

2.1. Methods overview

Suspected cases of drug-induced stuttering were initially identified and flagged in a previous investigation of developmental stuttering using EHRs at Vanderbilt University Medical Center (VUMC). Specifically, Pruett et al. (2021) used a keyword search of clinical notes followed by a text-mining algorithm and manual chart review to identify and validate developmental stuttering cases within approximately three million de-identified patient records. This multi-step approach was used to highlight potential cases since stuttering is not well-captured by International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and −10) codes and other traditional EHR phenotyping approaches. For example, in the United States, developmental stuttering is typically diagnosed and treated in schools and private specialty clinics and in those instances, stuttering billing codes may not be present in a medical system EHR. See Fig. 1 for a schematic depiction of the case identification process.

The keyword search and text-mining algorithm resulted in 1567 "high-likelihood" stuttering records, all of which were manually reviewed, resulting in 1143 confirmed developmental stuttering cases. Of the 424 records excluded during manual review, 40 were marked as possible drug-induced stuttering cases, an exclusionary criteria for the investigation of developmental stuttering. This study

examines those 40 suspected drug-induced stuttering cases in detail.

2.2. Data source – the synthetic derivative (SD) of the Vanderbilt University Medical Center EHR

Vanderbilt University Medical Center (VUMC) is a large academic medical center in Nashville, Tennessee and includes Vanderbilt University Hospital, Monroe Carell Jr. Children's Hospital, and over 100 primary care and specialty care outpatient clinics throughout the greater Nashville area. VUMC maintains a deidentified EHR database specifically for research purposes called the Synthetic Derivative (SD) with Health Insurance Portability and Accountability Act (HIPAA) identifiers removed (Danciu et al., 2014). At the time of this study, the SD contained roughly 3.1 million unique patient records extracted from the major VUMC EHR databases. At the time of the data pull for this study, the majority of patient records were from the years 2000 to 2021; however, there are occasional instances of records from the 1990s (Roden et al., 2008).

The SD records include basic demographic and clinical data such as billing and procedure codes, prescriptions, lab test results, and unstructured text from medical notes. Medical notes provide a flexible and efficient format for medical providers to document context necessary for understanding clinical encounters in the EHR including a patient's: medical history, primary complaint, test results, diagnosis, follow-up plans, and discussion of other applicable social and familial context (Rosenbloom et al., 2011). Additionally, email, mail, and telephone transcripts between patients and providers are also included within medical notes. This project was approved by and received non-human subjects designation from the VUMC Institutional Review Board.

2.3. Review of suspected drug-induced stuttering cases

The 40 suspected drug-induced stuttering cases were reviewed by a stuttering expert (PhD in communication sciences and disorders with focus in stuttering) and clinical pharmacist to evaluate the following: a) level of evidence for the implicated drug as a causal agent (specific approach described in Section 2.3.1), b) name, class, and mechanism of action of suspected drug, c) other drugs present surrounding the instance of stuttering, d) therapeutic measures including removal of drug, increase/decrease dosage, or initiation of new drug, and e) progression or remission of stuttering. Each record was adjudicated by both reviewers independently. The concordance of adjudicated results for variables a-e was estimated and discordant results were discussed and resolved by agreement and joint review. Additionally, a literature search was conducted for each implicated drug to determine whether the drug had been previously associated with stuttering in any case studies or reviews.

2.3.1. Naranjo Adverse Drug Reaction Probability Scale

A modified Naranjo Adverse Drug Reaction (ADR) Probability Scale, also known as the Naranjo Scale, was calculated to evaluate the level of evidence for the implicated drug as a causal agent. The Naranjo Scale is a questionnaire-based standardized method for assessing the probability of causal relationships between an adverse drug reaction and exposure to a drug (Naranjo et al., 1981). The scale was originally designed for use in controlled trials, but is also commonly applied in routine clinical practice (Kane-Gill et al., 2005; Liang et al., 2014; Seger et al., 2013). The scale consists of 10 questions that can be answered *yes, no*, or *do not know* with varying point values (−1, 0, +1 or +2) assigned to each answer based on the question. Total scores for these questions can range from −4 to +13. Based on this method, the adverse drug reaction is considered *definite* if the score is 9 or higher, *probable* if the score is 5 to 8, *possible* if the score is 1 to 4, and *doubtful* if the score is 0 or less. The 10 questions on the Naranjo Scale are listed below (see Supplemental Table 1 for full scale):

1. *Are there previous conclusive reports on this reaction?*
2. *Did the adverse event appear after the suspected drug was administered?*
3. *Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?*
4. *Did the adverse event reappear when the drug was re-administered?*
5. *Are there alternative causes (other than the drug) that could on their own have caused the reaction?*
6. *Did the reaction reappear when a placebo was given?*
7. *Was the drug detected in blood (or other fluids) in concentrations known to be toxic?*
8. *Was the reaction more severe when the dose was increased or less severe when the dose was decreased?*
9. *Did the patient have a similar reaction to the same or similar drugs in any previous exposure?*
10. *Was the adverse event confirmed by any objective evidence?*

(Naranjo et al., 1981)

Given the nature of the data available in the EHR, Question 6, "*Did the reaction reappear when a placebo was given?*" and Question 7, "*Was the drug detected in blood (or other fluids) in concentrations known to be toxic?*" were removed from consideration and the modified eight-question Naranjo scale was used to evaluate suspected cases of drug-induced stuttering. Possible scores from the modified scale can range from −3 to 11. Notably, the score thresholds on the original scale for determining *definite, probable, possible*, and *doubtful* reactions were maintained to employ a conservative approach that would not overestimate the probability of an adverse drug reaction.

To calculate the Naranjo score, keywords related to stuttering (i.e., stutter, stuttering, stammer, stammering, studder (*sic*), studdering (*sic*), disfluency, dysfluency) were searched within the EHR medical notes for the 40 suspected cases. Reviewers recorded demographic information, suspected drug name, reason for prescription, time of stuttering onset, history of stuttering, other drugs concurrently administered, and progression/remission of stuttering. The strength of the Naranjo scale is its simplicity for assessing

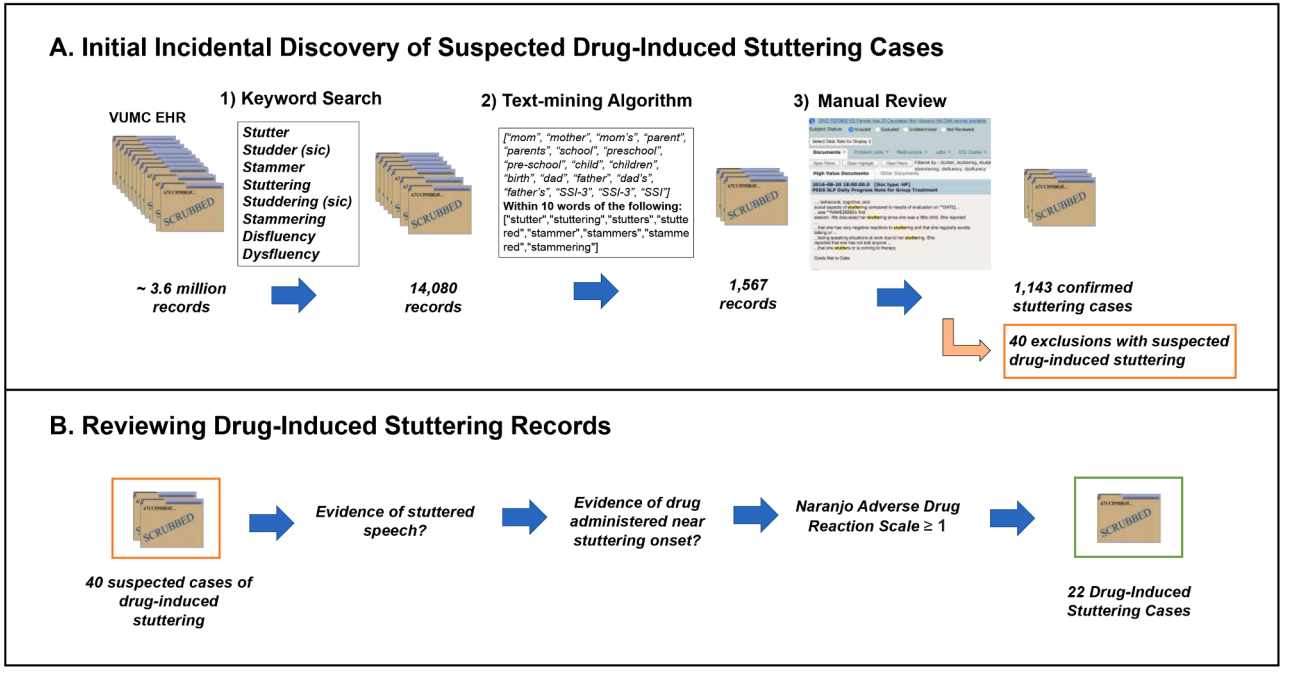

Fig. 1. Schematic Depicting Drug-Induced Stuttering Case Identification.

causality, but importantly, the questions are not weighted for the most integral elements of adverse drug reaction. In this study, the Naranjo scale is used as a broad criterion as opposed to a comprehensive objective conclusion.

Drug names, classification, and mechanism of action were reported using the National Library of Medicine NIH DailyMed online database. The DailyMed database contains information for FDA-approved products, including prescription and nonprescription medications, for public use. This information includes "boxed warnings, indications, dosage and administration, contraindications, warnings and precautions, adverse reactions, drug interactions, information about use in specific populations, and other important information for healthcare practitioners" (National Library of Medicine—About DailyMed, 2024). This drug information can be found in duplicate in diverse resources across the web, including additional public and private databases (Hochstein et al., 2009). For an in-depth description of the National Library of Medicine drug information resources, see Hochstein et al. (2009).

For this study, National Library of Medicine NIH DailyMed queries occurred in April 2024. Generic drug names were queried, except in two instances (somatotropin [Genotropin]; ribavarin [Virazole]) where the brand name was queried because an existing entry for the generic drug name could not be found. The first result matching the queried drug was directly quoted from the "Clinical Pharmacology" section, with occasional truncation for brevity and clarity (see Table 2).

3. Results

After independent review, 22 (55 %) of the 40 suspected cases were considered possible drug-induced stuttering cases. Based on the Naranjo scale, four cases were considered *probable* and 18 cases were considered *possible*. The remaining 18 excluded cases were considered *doubtful*. Exclusion reasons included lack of evidence for a drug administered near onset of stuttered speech (n= 16), lack of documentation of stuttered speech (n= 1), and a rare hereditary movement disorder complicating diagnosis (n= 1). Of the 22 cases (mean age = 35.9, SD = 21.7), 15 were female (mean age = 38.9, SD = 19.8), 7 were male (mean age = 29.4, SD = 25.7), and 8 (36 %) were younger than 18 years of age. All suspected pediatric cases reported onset occurring after eight years of age, beyond the typical age of onset for developmental stuttering. Race and ethnicity were inconsistently reported within the EHR (see Table 1). Prior to 2022, race and ethnicity were recorded via third party, leading to a high incidence of reporting error within the VUMC SD. VUMC has since added a detailed race/ethnicity self-report section to capture more accurate and specific race and ethnicity information. However, many current and former patients do not have this updated information available.

The median duration of the medical record for male and female drug-induced stuttering cases was largely similar (male median duration: 12 years, 1.7 months; female median duration: 11 years, 11.5 months). In contrast, the 18 records ultimately deemed *not* to be drug-induced stuttering cases had a median medical record duration of 5 years, 0.8 months. This discrepancy in duration of the medical record between confirmed cases and exclusions demonstrates that, in general, confirmed cases had more robust medical record documentation.

Overall, 18 different drugs were suspected of causing stuttering in 22 cases (see Table 2). Thirteen (59 %) of the 22 cases involved 1) drugs previously implicated in drug-induced stuttering case studies and/or 2) drugs reported to induce stuttering within adverse drug reporting databases (Nikvarz & Sabouri, 2022; Trenque et al., 2021). Four additional cases implicated drugs that had been listed as "concomitant" drugs in previous studies, or drugs prescribed at or near the onset of stuttering but not suspected of being causal in those studies. The most common drug classes implicated were antiseizure agents (implicated in 8 cases), central nervous system stimulants (implicated in 4 cases), and antidepressants (implicated in 4 cases). Cardiovascular related drugs were implicated in two cases, with the remaining drug classes each implicated in one case: antiviral, growth hormone, asthma/allergy related (leukotriene), antipsychotic, and opioid.

Among the 18 drugs, topiramate, an antiseizure medication, was implicated in four cases and methylphenidate, a central nervous system stimulant, was implicated in two cases (See Fig. 2). No other drug was implicated more than once. One case was linked to two different drugs (hydrocodone and phenytoin). No clear and consistent pattern emerged from the mechanism of action of implicated drugs; however, effects on GABA, glutamate, norepinephrine, serotonin and dopamine neurotransmitters and receptors were observed across multiple drugs and drug classes (see Table 2). Therapeutic measures included the removal of the suspected drug in 13 cases, a decrease in dosage of the suspected drug in 3 cases, and no specific mention of therapeutic measures were reported for the other 6 cases.

Text-based description of stuttered speech varied between cases but was generally limited. The following excerpts from EHR medical notes have a moderate level of description, reporting stuttering speech, suspected medication, therapeutic measure taken, and some context for progression of stuttering. Details related to dates, age, sex, and family status have been altered to prevent possible patient identification. For consistency, drugs are identified by their generic names rather than their brand names; brackets in the excerpts below indicate the generic name was substituted for the brand name.

Table 1
Demographics of Drug-Induced Stuttering Cases.

	Number of Cases	Age [mean (SD)]	*Race	*Ethnicity
Male	7	29.4 (25.7)	2 White, 5 not reported	7 not reported
Female	15	38.9 (19.8)	8 White, 2 African American, 5 not reported	6 non-Hispanic, 9 not reported
All	22	38.4 (21.1)	10 White, 2 African American, 10 not reported	6 non-Hispanic, 16 not reported

* Race and ethnicity are 3rd party reported within the EHR.

Table 2
Summary of Drugs Implicated in Drug-Induced Stuttering Cases.

EHR Chart Review for Possible Drug-Induced Stuttering Cases

Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
1	Female	not reported	not reported	topiramate (Topamax)	Antiseizure agent	"…Evidence suggests that topiramate (Topamax)…blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme…" (National Library of Medicine NIH DailyMed, last updated 2021)	Diazepam (Valium), Valproate (Depakote), Haloperidol (Haldol)	Removal	3 (possible)	Yes (Trenque et al., 2021)
2	Female	not reported	not reported				n/a	none reported	7 (probable)	Yes (Trenque et al., 2021)
3	Female	White	Non-Hispanic				Pimozide	Removal	5 (probable)	Yes (Trenque et al., 2021)
4	Female	African-American	Non-Hispanic				Atomoxetine, risperidone (Risperdal), lamotrigine (Lamictal), gabapentin (Neurontin)	none reported	3 (possible)	Yes (Trenque et al., 2021)
5	Female	African-American	Non-Hispanic	lamotrigine (Lamictal)	Antiseizure agent	"The precise mechanism(s) …are unknown… One proposed mechanism… involves an effect on sodium channels… lamotrigine (Lamictal) inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate)." (National Library of Medicine NIH DailyMed, last updated 2021)	Diazepam (Valium)	Removal	3 (possible)	Yes (Catania et al., 1999)
6	Female	White	Non-Hispanic	Clonazepam (Klonopin)	Benzodiazepine; Antiseizure agent, anticonvulsant, anxiolytic	"The precise mechanism by which clonazepam exerts its antiseizure and antipanic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system." (National Library of Medicine NIH DailyMed, last updated 2024)	Carbamazepine (Tegretol)	Removal	3 (possible)	No [listed as a concomitant in 3 cases reviewed by Nikvarz and Sabouri (2022)]
7	Female	White	not reported	gabapentin (Neurontin)	Antiseizure agent, GABA analog	"The precise mechanisms… are unknown. gabapentin	Pregabalin (Lyrica), topiramate (Topamax)	Removal	3 (possible)	Yes (Nissani & Sanchez, 1997)

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Table 2 (*continued*)

EHR Chart Review for Possible Drug-Induced Stuttering Cases

Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
						(Neurontin) is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. In vitro studies have shown that gabapentin (Neurontin) binds with high-affinity to… voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin (Neurontin) is unknown." (National Library of Medicine NIH DailyMed, last updated 2016)	(Topamax) [not suspected of possible cause of stuttering]			
8	Female	White	Non-Hispanic	Phenytoin (Dilantin); Hydrocodone (Hysingla)	Antiseizure agent; Opioid analgesic	Phenytoin: "The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas…" (National Library of Medicine NIH DailyMed, last updated 2013); Hydrocodone: "Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is	n/a	Removal (of hydrocodone)	5 (probable)	Yes (Ekici et al., 2013; McClean & McLean, 1985)

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Table 2 (*continued*)

EHR Chart Review for Possible Drug-Induced Stuttering Cases										
Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
						not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding." (National Library of Medicine NIH DailyMed, last updated 2008)				
9	Female	White	Non-Hispanic	Amitriptyline (Elavil)	Antidepressant	"… Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically, this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline." (National Library of Medicine NIH DailyMed, last updated 2023)	gabapentin (Neurontin)	Decrease dosage	3 (possible)	No [listed as a concomitant in 1 case reviewed by Nikvarz and Sabouri (2022)]
10	Female	White	not reported	Citalopram (Celexa)	Antidepressant	"The mechanism of action of citalopram as an antidepressant is unclear, but is presumed to be related to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT)." (National Library of Medicine NIH DailyMed, last updated 2023)	Levetiracetam [antiseizure medication]	Removal	3 (possible)	No [listed as a concomitant in 2 cases reviewed by Nikvarz and Sabouri (2022)]
11	Female	not reported	not reported	Fluoxetine (Prozac)	Antidepressant	"Although the exact mechanism of fluoxetine is unknown, it is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin." (National Library of	n/a	Removal	1 (possible)	No [listed as a concomitant in 2 cases reviewed by Nikvarz and Sabouri (2022)]

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Table 2 (*continued*)

EHR Chart Review for Possible Drug-Induced Stuttering Cases

Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
						Medicine NIH DailyMed, last updated 2023)				
12	Female	White	not reported	Escitalopram (Lexapro)	Antidepressant	"The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT)." (National Library of Medicine NIH DailyMed, last updated 2021)	Chemotherapy medications: Doxorubicin (Adriamycin), Cyclophosphamide (Cytoxan), Paclitaxel (Taxol)	none reported	2 (possible)	No
13	Female	not reported	not reported	Lisdexamfetamine (Vyvanse)	CNS stimulant	"Lisdexamfetamine is a prodrug of dextroamphetamine.	n/a	Decrease dosage	5 (probable)	No
14	Male	not reported	not reported			Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD and BED is not known." (National Library of Medicine NIH DailyMed, last updated 2023)	n/a	Removal	1 (possible)	No
15	Male	not reported	not reported	Dextroamphetamine-amphetamine (Adderall)	CNS stimulant	"Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in…ADHD is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space." (National Library of Medicine NIH DailyMed, last updated 2023)	n/a	none reported	2 (possible)	Yes (Donaher et al., 2009)
16	Male	White	not reported	Methylphenidate (Concerta)	CNS stimulant	"Methylphenidate hydrochloride is a CNS stimulant. The mode of therapeutic action in ADHD is not known… Methylphenidate blocks the reuptake of norepinephrine and dopamine into the	Atomoxetine (Strattera) [SSRI]	none reported	1 (possible)	Yes (Trenque et al., 2021)

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Table 2 (*continued*)

EHR Chart Review for Possible Drug-Induced Stuttering Cases

Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
						presynaptic neuron and increases the release of these monoamines into the extraneuronal space." (National Library of Medicine NIH DailyMed, last updated 2024)				
17	Female	White	Non-Hispanic	Ranolazine (Ranexa)	Cardiovascular agent [Antianginal agent]	"…Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure… at therapeutic levels can inhibit the cardiac late sodium current (INa). However, the relationship of this inhibition to angina symptoms is uncertain. The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of IKr, which prolongs the ventricular action potential." (National Library of Medicine NIH DailyMed, last updated 2010)	Ropinirole (Requip) [dopamine agonist (anti-Parkinson)]; Diazepam (Valium) [anticonvulsant, anxiolytic]	Decrease dosage	3 (possible)	No
18	Male	not reported	not reported	Droxidopa (Northera)	Cardiovascular agent [Alpha and Beta-adrenergic agonists]	"… Droxidopa is a synthetic amino acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, which is extensively distributed throughout the body. Droxidopa is believed to exert its pharmacological effects through norepinephrine… Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction. Droxidopa… induces small and transient rises in plasma norepinephrine." (National Library of Medicine NIH DailyMed, last updated 2021)	Phenelzine (Nardil) [antidepressant monoamine oxidase inhibitor]; Pregabalin (Lyrica) [antiseizure agent, GABA analog]	Removal	2 (possible)	Yes (Donaher et al., 2009)
19	Female	not reported	not reported	Montelukast (Singulair)	Leukotriene receptor antagonist [asthma/allergy]	"The cysteinyl leukotrienes (LTC 4, LTD 4, LTE 4) are products of arachidonic acid metabolism and are released from various cells,	n/a	Removal	1 (possible)	No

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Table 2 (*continued*)

EHR Chart Review for Possible Drug-Induced Stuttering Cases										
Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
						including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT 1) receptor is found in the human airway… and on other pro-inflammatory cells… CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT 1 receptor… Montelukast inhibits physiologic actions of LTD 4 at the CysLT 1 receptor without any agonist activity." (National Library of Medicine NIH DailyMed, last updated 2021)				
20	Male	not reported	not reported	olanzapine (Zyprexa)	Antipsychotic	"The mechanism of action of olanzapine (Zyprexa)… is unclear. However, the efficacy of olanzapine (Zyprexa) in schizophrenia could be mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism." (National Library of Medicine NIH DailyMed, last updated 2023)	n/a	Removal	1 (possible)	Yes (Bar et al., 2004)
21	Male	White	not reported	Somatotropin (Genotropin)	Growth hormone	"[Somatotropin] is therapeutically equivalent to human growth hormone of pituitary origin and achieves similar pharmacokinetic profiles in normal adults. In pediatric patients who have growth hormone deficiency (GHD), have Prader-Willi syndrome (PWS), were born small for gestational age (SGA), have Turner syndrome (TS), or have Idiopathic short stature (ISS), treatment with [somatotropin] stimulates linear growth…" (National Library of	n/a	Removal	1 (possible)	No

(*continued on next page*)

Table 2 (*continued*)

EHR Chart Review for Possible Drug-Induced Stuttering Cases

Case ID	Sex	Race	Ethnicity	Suspected Drug: Drug name (Brand name)	Drug Class	Mechanism of Action[a]	Concomitant Drugs of Interest	Therapeutic Measure Taken	Naranjo Adverse Drug Reaction Probability Scale Score	Previously Implicated in Drug Induced Stuttering?
22	Male	not reported	not reported	Pegylated interferon/ ribavarin (Virazole)	Antiviral [synthetic nucleoside]	Medicine NIH DailyMed, last updated 2023) "In cell cultures the inhibitory activity of ribavirin for respiratory syncytial virus (RSV) is selective. The mechanism of action is unknown. Reversal of the in vitro antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites… In addition to the above, ribavirin has been shown to have in vitro activity against influenza A and B viruses and herpes simplex virus, but the clinical significance of these data is unknown." (National Library of Medicine NIH DailyMed, last updated 2019)	gabapentin (Neurontin)	none reported	1 (possible)	No

[a] Source: Clinical Pharmacology section of the National Library of Medicine NIH DailyMed website (accessed April 2024).

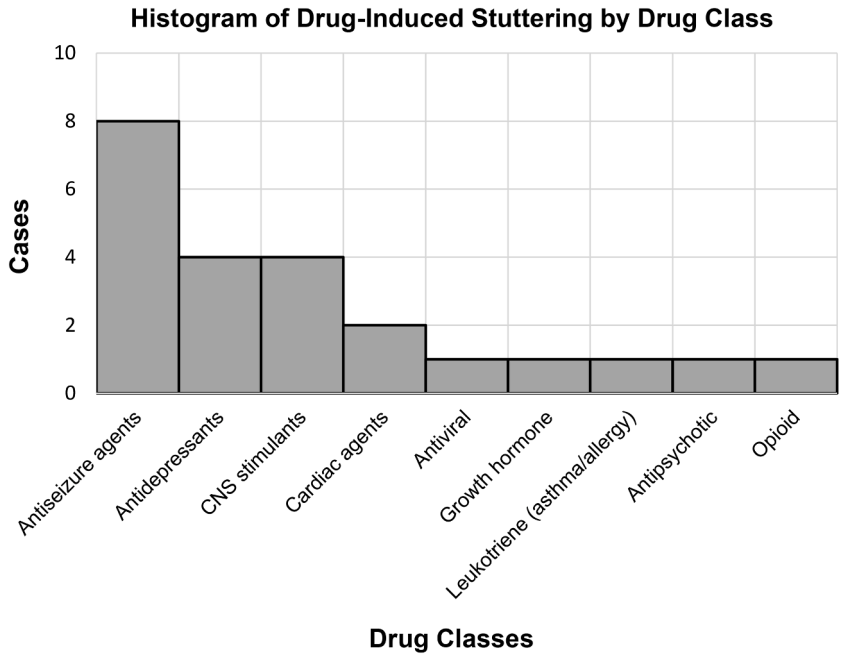

Fig. 2. Drug Types Implicated in Drug-Induced Stuttering Cases.

> "Reports that [he/she] developed some stuttering after initiating [fluoxetine]. Took a break over the summer. Weaned off of [fluoxetine] in **DATE** and now planning to resume. Since increase in [fluoxetine], [he/she] has not had any panic attacks and [his/her] stuttering has improved."

> "Today, I saw *[NAME]* for follow-up of [his/her] epilepsy. [He/she] had a recent exacerbation after being sleep deprived and very stressed, anxious and almost phobic with storms. The [citalopram] provided [his/her] relief but this was discontinued due to stuttering as a possible side effect."

In contrast, the following medical note excerpts provide less overall description: some reporting of stuttered speech but no description of therapeutic measures or progression of stuttering.

> "Since increasing [his/her] dose [topiramate], [he/she] has been losing [his/her] train of thought. [He/she] has also started to stutter and struggle to 'get words out.' [He/she] is not remembering things very well."

> "Singulair [montelukast] per [parent] medication affected patient's speech causing [him/her] to stutter…"

In several cases, healthcare providers seemed hesitant to ascribe new onset of stuttering to a drug side effect. The following medical note excerpts demonstrate provider uncertainty.

> "Pt reports [he/she] began stuttering and having pain in [his/her] [torso] about 3 days ago - also c/o weakness and still having tremors. Pt concerned about the stuttering - wonders if medication [clonazepam] may be causing? MD not sure that the stuttering is from meds."

> "… [he/she] is **AGE[birth-12] years old about 1 1/2 years ago [he/she] started stuttering but it is intermittent and not all the time. [Parent] thinks this coincided with [him/her] starting growth hormone. I don't know what to make of the stuttering since [he/she] does not do it all the time… I don't know if the growth hormone has anything to do with the stuttering… [Parent] had decided to stop the GH injections because *[NAME]* was having frequent, severe headaches… [He/she] has not had any further headaches since stopping the medication… [He/she] continues to have problems with stuttering… [He/she] continues to receive OT services."

> "…[He/she] was started on olanzapine scheduled qhs in addition to PRN doses. [He/she] felt the PRN olanzapine was more beneficial in controlling [his/her] anxiety than [his/her] PRN ativan. [His/her] scheduled olanzapine was titrated to 10 mg qhs and [he/she] continued to use PRN doses throughout the day; [he/she] did complain that the olanzapine was causing [him/her] to stutter and slur [his/her] words, although the team felt that this was more likely due to anxiety as patient did not demonstrate any dysphasia on interview or per collateral. [He/she] otherwise tolerated the olanzapine well without side effects and experienced improvement in the disorganization of [his/her] thoughts, insight, and anxiety…"

Overall, cases that were characterized by a lack of detailed reporting and follow-up received lower scores on the Naranjo Scale and diagnostic uncertainty.

4. Discussion

Suspected cases of drug-induced stuttering were associated with a variety of drugs within the EHR. Using the National Library of Medicine NIH DailyMed classification, the most common drug classes included antiseizure medications, central nervous system stimulants, and antidepressants. The drug classes associated with drug-induced stuttering in this study largely mirror previous studies. For example, Trenque et al. (2021) reported antiepileptics, antidepressants, antipsychotics, and sympathomimetic agents among the most frequently implicated drugs. These psychoactive substances are designed to interact with the autonomic and central nervous systems and, in turn, perturbation of speech-motor pathways within the brain by chemical agents may lead to stuttering. The impact of psychotropic medications on speech fluency has been previously documented (Maguire et al., 2020); however, the mechanism of action for these implicated drug classes remains unclear. Despite preliminary evidence supportive of a relationship between the identified drug classes and stuttered speech in previous studies, there remained clinical hesitation to ascribe a causal relationship between the drug exposure and new onset of stuttering in most cases. This suggests clinicians may not be aware of the potential for drug-induced stuttering. This is in part evidenced through sparse description of drug-induced stuttering within the EHR. Further, this lack of description is a limitation of this study as it could reflect deflated Naranjo Scale scores across cases due to lack of information opposed to clearly assigned responses. Despite this limitation, the results are representative of everyday clinical treatment practices and suggest an improved understanding of this potential adverse event would benefit clinicians.

4.1. Speech-motor pathways affected by implicated drug classes

Speech production is a complex sensorimotor process requiring coordination of multiple brain areas, combining semantic, linguistic, and phonological processing with speech motor control (Riecker et al., 2000). Speech motor control requires coordination of respiration, phonation, and articulation with integration of motor, somatosensory, and auditory information (Kearney & Guenther, 2019). Disfunction in connections between the cerebral cortex, basal ganglia, and thalamus, termed the cortico-basal ganglia-thalamocortical (CBTC) loop, has been studied in the pathogenesis of both developmental stuttering and neurogenic stuttering and may provide a model for drug-induced stuttering (Alm, 2004; Chang & Guenther, 2020; Lu et al., 2010; Nikvarz & Sabouri, 2022; Theys et al., 2013).

The basal ganglia, a collection of subcortical nuclei, affect the motor cortex via pathways through the thalamus and aid the planning and execution of smooth movements (Freeze et al., 2013). Broadly, the motor cortex receives input from the basal ganglia via two distinct pathways: the direct and indirect pathways. Overall, the direct pathway is excitatory and stimulates the motor cortex while the indirect pathway inhibits the motor cortex and other competing motor programs. It has been proposed that a balance of excitation and inhibition is necessary for normal motor program execution and disturbing the output from direct or indirect pathways can result in issues associated with motor control (Conn et al., 2005).

The neurotransmitters GABA, glutamate, and dopamine play a role in the CBTC loop and can inhibit or disinhibit speech-motor activity, depending on the specific pathway and nuclei (Calabresi et al., 2014). topiramate, the drug most commonly implicated in drug-induced stuttering in this study and primarily prescribed for epilepsy and migraines, is a carbonic anhydrase inhibitor that modulates GABA and glutamate (Lyseng-Williamson & Yang, 2007). Among other mechanisms of action, topiramate enhances GABAergic inhibition and reduces excitatory glutamatergic signaling, potentially disrupting the balance between direct and indirect pathways necessary for smooth speech execution (White, 2005). topiramate has known side-effects including word-finding difficulties, slurred articulation, and slowed, effortful speech (Donegan et al., 2015; Marino et al., 2012; Ojemann et al., 2001; Rosenfeld, 1997). While stuttering is not specifically listed as a known side-effect, studies of pharmacovigilance databases have shown topiramate to be among the common contributors to drug-induced stuttering (Ekhart et al., 2021; Trenque et al., 2021).

Dopamine also plays a modulating role in the direct and indirect pathways. In the direct pathway, dopamine has an excitatory effect via D1-type dopamine receptors; in the indirect pathway, dopamine has an inhibitory effect via D2-type dopamine receptors (Gerfen, 2023). Some antipsychotic drugs that block dopamine, such as haloperidol and risperidone, have been reported to *decrease* stuttering in patients with developmental stuttering (Maguire et al., 2021; Wu et al., 1997). Understanding the nuanced role of dopamine in motor pathways has helped elucidate the pathophysiology of several motor disorders and lead to targeted therapeutic interventions. For example, Parkinson's disease results in dopamine depletion in the substantia nigra of the basal ganglia, leading to hypokinetic symptoms due to excessive indirect pathway activity and insufficient direct pathway activation (Murdoch, 2010). Additionally, studies have demonstrated a link between the administration of levodopa, a drug used as a dopamine replacement agent, and the occurrence of stuttering in Parkinson's disease. Data from these studies largely support a dualistic model, proposing that speech disfluencies may be related to both increase or decrease in dopamine levels (Goberman et al., 2010; Goberman & Blomgren, 2003; Im et al., 2019; Tsuboi et al., 2019; Tykalová et al., 2015). A similar imbalance between the direct and indirect pathways due to exogenous drugs may underlie drug-induced stuttering.

Given the complex role GABA, glutamate, and dopamine play in the direct and indirect pathways of speech motor control, the variety of drugs implicated in drug-induced stuttering is not entirely surprising: any drugs altering the excitatory-inhibitory balance of the pathways may lead to abnormal speech motor control.

4.2. Other brain areas implicated in stuttering

As detailed in Neef and Chang (2024), in addition to speech-motor pathway models, studies of adults and children who stutter have suggested a number of differences in brain structure and function including cortical regions (e.g., Kell et al., 2018; Preibisch et al.,

2003; Watkins et al., 2008), subcortical structures (e.g., Giraud et al., 2008; Sitek et al., 2016; Watkins et al., 2008), the limbic system (e.g., Neef et al., 2018; Toyomura et al., 2018), and gray and white matter structures (e.g., Connally et al., 2014; Johnson et al., 2022; Kronfeld-Duenias et al., 2016; Neef, Anwander et al., 2018). For a more comprehensive review of stuttering imaging literature, see Chang et al. (2019), Connally et al. (2018), Neef et al. (2015), and Neef and Chang (2024)

One recent study examined acquired stuttering caused by focal brain damage and found heterogeneous brain lesions causing stuttering that were functionally connected via a common network (Theys et al., 2024). The stuttering network included the left putamen, claustrum, amygdalostriatal transition area, and adjacent areas. The involvement of the amygdala in the stuttering network may help explain cases of drug-induced stuttering involving selective serotonin reuptake inhibitor antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for both depression and anxiety disorders. A large body of evidence has shown that the amygdala plays a key role in fear conditioning and the brain region is linked to anxiety disorders (Davidson, 2002; LeDoux, 2003; Rauch et al., 2003; Walf & Frye, 2006). Studies also suggest that the anxiolytic effect of SSRIs is mediated by the amygdala (Inoue et al., 2004). However, initial SSRI treatment may paradoxically increase symptoms of anxiety prior to providing therapeutic effects (Burghardt & Bauer, 2013). Additionally, Toyomura et al. (2018) found that for adults who stutter, increased amygdala activity was correlated with stuttering frequency. So, although the role of the amygdala in speech production is not clearly understood, the involvement of the amygdala in the stuttering network and as a target of SSRIs provides a possible mechanism for the effect of SSRIs on speech fluency.

4.3. Potential sex differences in drug-induced stuttering

While stuttering is a male-dominated trait in adulthood, a greater proportion of females (2.14 female to male ratio) were affected by drug-induced stuttering in this study. Pharmacovigilance database reviews also found females were affected by drug-induced stuttering at higher rates (1.39 female to male ratio in Trenque et al. [2021] and 1.33 female to male ratio in Ekhart et al. [2021]). One explanation may be that females are prescribed psychotropic medications more frequently than males, thereby increasing the probability of experiencing drug induced stuttering (Simoni-Wastila, 1998). To illustrate this point, within the VUMC EHR, 77.5 % of prescriptions for topiramate, the medication most frequently identified as a probable cause of stuttering in this study, were to individuals of EHR-reported female gender. However, this was not the case for methylphenidate, the second-most frequently identified probable cause of stuttering, where 43.5 % of prescriptions in the EHR were to individuals of EHR-reported female gender. Given our sampling method, we cannot definitively conclude that differences in prescription rates by gender are responsible for the observed disparity, but it may in part explain the female bias in drug-induced stuttering.

Increased healthcare utilization in females relative to males may also be a contributing factor to this bias (Mustard et al., 1998). In general, higher healthcare utilization by females may result in not only higher rates of prescriptions for the same conditions, but also a greater number of healthcare encounters where pathologies may be documented.

Finally, another hypothesis is that people who stutter in childhood but recover may have a lower threshold for “dysregulation” or “interference” within their speech-motor system and thus may be more susceptible to developing acquired stuttering (Shahed & Jankovic, 2001). Compared to males, more females recover from stuttering in early childhood, so there may be more adult females susceptible to drug-induced stuttering. Unfortunately, these inquiries are beyond the scope of this study to evaluate but should be considered in future study designs.

4.4. Opportunities to increase documentation within the EHR

One finding from this review was a lack of comprehensive documentation of drug induced stuttering within the EHR, which contributed to limited evidence for implicated drugs leading to stuttering. The issue of documentation is not necessarily confined to this study: Nikvarz and Sabouri (2022) found similarly poor reporting of stuttering behaviors, timing between initiation of drug and onset of stuttering, therapeutic measures, and improvement or progression of stuttering within case studies. When calculating the Naranjo Scale, the *do not know* response is intended to be used sparingly; however, the limited documentation in the present study lead to all cases having at least one response of *do not know*. Additional follow-up reports indicating the resolution or continuance of stuttering following therapeutic measures could clarify the impact of the implicated drug on stuttering. In addition to limited Naranjo Scale details, there was also limited documentation of specific stuttering characteristics such as the type of stuttering observed (repetitions, prolongations, blocks, etc.), frequency of stuttering, and the patient’s psychological state. Anticipation and avoidance of stuttering are common elements of developmental stuttering and presence or absence of these characteristics within drug-induced stuttering may help us understand if, as some suspect, these are learned behavioral aspects of developmental stuttering (Jackson et al., 2018, 2019).

Follow-up is especially important when cases are complicated by multiple psychoactive drugs. While stuttered speech was the most prominent symptom in most cases, some cases had other side effects such as headache, trembling (non-specific), etc. Given the medications prescribed and baseline condition of the patients, it is difficult to conclude that all side effects were related to the same medication. Consequently, the concomitant drugs in this study warrant further investigation, particularly when given in combination with the primary suspected drug.

To fully characterize instances of drug-induced stuttering, medical professionals should be aware of the potential for pharmacogenic effects and thoroughly document the onset, progression, and resolution of the condition. Increasing collaboration between medical providers and speech-language pathologists could provide a more complete evaluation of suspected cases of drug-induced stuttering. In this study, we did not observe consultation or referral to speech language pathology for any cases. Raising awareness

of drug-induced stuttering may ultimately uncover far more cases than previously assumed and facilitate clinical management when appropriate.

4.5. Study limitations

While this study provides novel insights into drug-induced stuttering within EHRs, there are important limitations to consider. First, VUMC psychiatric EHRs receive additional data protections and are largely unavailable for text-based chart review. These restrictions likely led to an under count of drug-induced stuttering cases involving psychotropic medications such as antidepressants and antipsychotics, which are traditionally prescribed by psychiatrists. Second, suspected drug-induced stuttering records were initially discovered using a text-mining process optimized for the identification of developmental stuttering cases. Therefore, certain keywords (i.e., "mother", "school", "SSI") used for identifying developmental stuttering cases may not be useful and could be exclusionary for detecting drug-induced stuttering. Consequently, this study likely underestimates the total number of cases; the number of drug-induced stuttering cases identified should not be viewed as the base rate of the condition across the entire EHR.

5. Conclusion

This study reviewed suspected cases of drug-induced stuttering within EHRs at VUMC. Antiseizure medications, central nervous system stimulants, and antidepressants were the most commonly implicated drug classes involved in drug-induced stuttering. In general, these drugs are designed to affect the brain and may impact the direct and indirect pathways of the cortico-basal ganglia-thalamocortical loop leading to changes in speech fluency. Other cases were associated with a variety of drug classes including cardiac agents, antivirals, growth hormone, leukotriene receptor agonists for asthma, antipsychotics, and opioids. topiramate, a drug with known effects on speech and language, was the drug associated with the most cases of drug-induced stuttering.

This study also revealed that many suspected cases of drug induced stuttering lacked details reporting speech characteristics, therapeutic intervention, and progression or resolution of stuttering. To increase knowledge of drug-induced stuttering and improve patient care, healthcare providers should be aware of the potential for drug-induced stuttering, especially with drugs that affect neurotransmission, and provide comprehensive evaluation and follow-up care. Further studies exploring the epidemiology and pharmacology of drug-induced stuttering are needed to characterize the prevalence and mechanism of action of the condition.

CRediT authorship contribution statement

Dillon G. Pruett: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christine Hunter:** Formal analysis, Data curation. **Alyssa Scartozzi:** Writing – review & editing, Writing – original draft, Data curation. **Douglas M. Shaw:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Shelly Jo Kraft:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Robin M. Jones:** Writing – review & editing, Supervision, Conceptualization. **Megan M. Shuey:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis. **Jennifer E. Below:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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