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Identifying Medications Underlying Communication Atypicalities in Psychotic and Affective Disorders: A Pharmacovigilance Study Within the FDA Adverse Event Reporting System

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# TITLE PAGE

## Identifying medications underlying communication

### atypicalities in psychotic and affective disorders:

#### A pharmacovigilance study within the FDA Adverse Event

#### Reporting System

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### 33 Abstract

34 **Purpose:** Communication atypicalities are considered promising markers of a broad  
35 range of clinical conditions. However, little is known about the mechanisms and  
36 confounders underlying them. Medications might have a crucial, relatively unknown  
37 role both as potential confounders and offering an insight on the mechanisms at  
38 work. The integration of regulatory documents with disproportionality analyses  
39 provides a more comprehensive picture to account for in future investigations of  
40 communication-related markers. The aim of the current study was to identify a list of  
41 drugs potentially associated with communicative atypicalities within psychotic and  
42 affective disorders.

43 **Method:** We developed a query using the Medical Dictionary for Regulatory  
44 Activities (MedDRA) to search for communicative atypicalities within the FDA  
45 Adverse Event Reporting System (FAERS, updated June 2021). A Bonferroni  
46 corrected disproportionality analysis (Reporting Odds Ratio) was separately  
47 performed on spontaneous reports involving psychotic, affective, and non-  
48 neuropsychiatric disorders, to account for the confounding role of different underlying  
49 conditions. Drug adverse event associations not already reported in the SIDER  
50 database of labeled adverse drug reactions (unexpected) were subjected to further  
51 robustness analyses to account for expected biases.

52 **Results:** A list of 291 expected and 91 unexpected potential confounding  
53 medications was identified, including drugs that may irritate (inhalants) or desiccate  
54 (anticholinergics) the larynx, impair speech motor control (antipsychotics), induce  
55 nodules (acitretin) or necrosis (VEGFR-inhibitors) on vocal cords, sedatives and  
56 stimulants, neurotoxic agents (antiinfectives), and agents acting on neurotransmitter  
57 pathways (dopamine agonists).

58 **Conclusions:** We provide a list of medications to account for in future studies of  
59 communication-related markers in affective and psychotic disorders. The current test  
60 case illustrates rigorous procedures for digital phenotyping, and the methodological  
61 tools implemented for large scale disproportionality analyses can be considered a  
62 roadmap for investigations of communication-related markers in other clinical  
63 populations.

64

## Introduction

65 The confounding role of medications on communication-related markers

66 Affective and psychotic disorders have long been associated with atypical

67 communicative patterns - e.g., decreased emotional expression and flat prosody

68 (Cummins et al., 2015; Parola et al., 2020). This awareness is widely used during the

69 assessment of the disorders, and is increasingly investigated through automated

70 voice and content analysis (Faurholt-Jepsen et al., 2018; Hansen et al., 2021; Low et

71 al., 2020; Parola, Lin, et al., 2022; Parola, Simonsen, et al., 2022). The combination

72 of new powerful forms of machine learning, pervasive smartphone data collection,

73 and other sources of big data will allegedly identify historically elusive markers for

74 affective and psychotic disorders and therefore enable more reliable diagnoses,

75 continuous evaluation of symptoms, and perhaps even personalized treatment

76 (Arevian et al., 2020; Ben-Zeev et al., 2019; Cohen, Cox, et al., 2020; Cohen,

77 Schwartz, et al., 2020; Insel, 2017). However, communication is a complex

78 phenomenon and its relation to specific disorders is not straightforward, with many

79 potential confounders and ethical considerations (Albuquerque et al., 2021; Corona

80 Hernández et al., 2023; Parola, Lin, et al., 2022; Rybner et al., 2022).

81 Medications, which are disproportionately associated with neuropsychiatric

82 diagnoses and their co-morbidities, can affect not only mental health but also the

83 communicative patterns in the patient. For example, commonly used medications

84 with anticholinergic effects (e.g., antihistamines and antidepressants) can cause

85 reduced salivation flow (xerostomia) and sedation of the mouth, which could cause

86 dysphonia and difficulty in articulation (Haft et al., 2015). Another example: high D2R

87 occupancy antipsychotics are administered to patients with psychotic disorders and

88 are also associated with slower speech and increased pauses (de Boer et al., 2020).  
89 Therefore, it is often not clear whether the communicative atypicalities identified as  
90 behavioral markers of affective and psychotic disorders could be partially  
91 confounded by medications. Unfortunately, more general investigations of the  
92 associations between communicative atypicalities and medications are still sparse,  
93 and no comprehensive overview is available (see Supplementary Material 1 –  
94 Section A for an overview of studies assessing the effect of medication on speech  
95 patterns in schizophrenia).

96 Therefore, the objective of the current study was to identify a list of drugs that  
97 could be associated with communicative atypicalities, which should be evaluated in  
98 the future as potential confounders in communication-related markers of affective  
99 and psychotic disorders. After introducing our two key sources of information–  
100 clinical-trial-based information (SIDER, Kuhn et al., 2016) and spontaneous reports  
101 (FAERS, FDA, 2022)–, four common causal mechanisms underlying observed  
102 associations between drugs and adverse events are briefly discussed. We present  
103 how the potential biases highlighted can be accounted for in the analyses before  
104 detailing materials and methods. Finally, the resulting list of drugs associated with  
105 communicative atypicalities are reported and discussed.

## 106 Information sources

107 As medications are tested in clinical trials, adverse drug reactions are  
108 evaluated, and if the drug is approved for market distribution (marketing  
109 authorization) these adverse reactions are reported by law in the insert of the  
110 medication package (Poluzzi et al., 2012), also known as prescribing information or  
111 summary of product characteristics. However, as the drug is used outside of clinical

112 trials (post-marketing phase) unexpected adverse drug reactions are often detected.  
113 For example, an adverse drug reaction could arise in populations not investigated in  
114 clinical trials (e.g., older or younger cohorts, pregnant women, patients with  
115 additional comorbidities). In addition, multiple drugs are often administered together  
116 (polytherapy), and an adverse drug reaction could arise from their interaction. Such  
117 suspected adverse reactions to drugs can be spontaneously reported to the  
118 regulatory agencies by physicians, marketing authorization holders, and the general  
119 public. Disproportionality analyses are statistical techniques developed to detect  
120 patterns within spontaneous reporting systems' databases in an attempt to provide a  
121 more comprehensive safety profile of medications (Alves et al., 2013).

122       Clinical trials and disproportionality analyses have complementary strengths.  
123 Clinical trials have obvious advantages, primarily that, by carefully selecting  
124 homogeneous samples and randomly distributing them across interventions, they  
125 remove many possible confounders and provide a strong causal assessment.  
126 Conversely, spontaneous reports can cover a much broader variety of patients and  
127 drug uses, including adverse reactions that are commonly underreported during  
128 clinical trials, although certain causality cannot be inferred due to confounders and  
129 lack of randomization. For instance, rashes are easy to observe, and arrhythmias  
130 could be fatal. Therefore, both are relatively prominent in clinical trial reports (Loke &  
131 Derry, 2001; Seruga et al., 2016) as compared with symptoms such as raspy vocal  
132 quality, or mispronunciations of speech sounds. However, communication  
133 impairments can be disabling from the patient's point of view, and therefore be more  
134 likely to be spontaneously reported, as has been shown for stuttering (Ekhart et al.,  
135 2021; Inácio et al., 2017; Toki & Ono, 2018; Trenque et al., 2021).



136           Pharmacovigilance has long acknowledged that spontaneous reports provide  
137 very noisy information riddled with well-known biases. For example, reports may be  
138 incomplete or duplicated, lack quality control of the information provided (e.g.,  
139 patients do not have the right language and knowledge to accurately describe their  
140 symptoms), contain potential biases, and may ignore external factors such as the  
141 novelty of a drug and how media coverage of adverse reactions affects the number  
142 of reports (Poluzzi et al., 2012; Raschi et al., 2018; Wisniewski et al., 2016). In other  
143 words, causal connections between drugs and adverse reactions should not be  
144 established based solely on spontaneous reports. Nevertheless, by taking these  
145 biases into account, disproportionality analyses can generate hypotheses for further  
146 investigation in analytical studies (cohort and case-control studies). Finally, with  
147 large enough sample sizes, there are methods for approximately estimating the  
148 causal effect of drugs in observational studies by adjusting for these newly  
149 considered confounders through confounding-adjustment methods (Hernán, 2018). It  
150 should be noted that package inserts and spontaneous reports do not exhaust the  
151 possible sources of information on adverse drug reactions, which would include, for  
152 instance, the scientific literature, health records, and clinical expertise in general.

### 153 Causal models underlying drug adverse event associations.

154           Disproportionality analyses identify adverse events that are more frequently  
155 present in reports about a given drug than in reports not containing that drug.  
156 However, the observed association could be generated through different causal  
157 mechanisms, with four common ones represented in **Figure 1**.

158           The first possible causal model is simply that the adverse event is indeed  
159 caused by the drug (an **Adverse Reaction** to it; DAG A). For example, administering

160 anticholinergic drugs often results in reduced salivation flow (xerostomia) and  
161 sedation of the mouth, which can cause speech impairment (Haft et al., 2015).

162         However, the association might also result from **Reverse Causality** (DAG B):  
163 the drug is taken because of the event (e.g., to treat it)<sup>1</sup>. For example, botulinum  
164 toxin is approved to treat spasmodic dysphonia, and antipsychotics are administered  
165 off-label to reduce stuttering (Maguire et al., 2020). These drugs can be reported as  
166 associated with a speech impairment because, for example, the lack of specific fields  
167 for symptoms of the underlying condition or for comorbidities often generates  
168 ambiguity in the reported information. Furthermore, when therapy does not reduce  
169 symptoms, reports might incorrectly record the indication for use (pre-existing  
170 stuttering) as an adverse reaction (after drug administration, stuttering is still there).

171         A third common possibility is the so-called “common cause” or fork (Pearl,  
172 2009). Here the underlying condition is causing both the prescription of the drug and  
173 the adverse event, without there being any direct causation between the latter two  
174 (**Confounding by Indication**; DAG C). For example, psychotic disorders can involve  
175 some degree of communication impairment (e.g., alogia, i.e., reduced and vague  
176 speech, or disorganized speech), as well as the administration of antipsychotics.  
177 Therefore, when assessing all reports on FAERS, one might find an association  
178 between communication impairments and antipsychotics simply due to their co-  
179 presence, even if there were no direct causal association. Another example of the  
180 “common cause” problem is seen with gastroesophageal reflux, for which proton  
181 pump inhibitors (PPI) are administered. Acid reflux can also affect the larynx and  
182 vocal cords, resulting in dysphonia (Lechien et al., 2017), which would then appear  
183 to be associated with PPI even in the absence of a direct causal link.

---

<sup>1</sup> While the adverse event is causing the prescription of the drug, the drug itself could be affecting the symptom (e.g., diminishing it) and therefore a more nuanced causal model than this simplified DAG would have to include bidirectional causal arrows, or a temporal dimension to causation.

184           A fourth common possibility is that the adverse event is indeed an adverse  
185 reaction, but to a different concomitant drug also prescribed due to the underlying  
186 condition (**Confounding by Concomitant**; DAG D). For example, diuretics are  
187 usually administered in conjunction with angiotensin-converting enzyme inhibitors  
188 (ACEI), which are known to cause bradykinin-related cough and laryngeal irritation.  
189 Therefore, diuretics might appear to be associated with dysphonia, even if the latter  
190 were exclusively due to ACEIs.

191           Finally, the relationship between a drug and an event may also not be  
192 reducible to one DAG only. Botulinum toxin may indeed be used to treat spasmodic  
193 dysphonia (DAG B), but it was also subject to a warning by the FDA because the  
194 systemic spread of the toxin can lead to temporary flaccid paralysis and related  
195 dysphonia (DAG A) (Kuehn, 2009).

## 196 From causal models to statistical analyses

197           When disproportionality analyses identify an association between a drug and  
198 an adverse event, how can one discriminate between the possible causal  
199 mechanisms? It turns out that there is no replacement for clinical and scientific  
200 knowledge, including evidence from previous studies, clinical expertise, and  
201 informed mechanistic hypotheses. This knowledge must play a meta-statistical role  
202 in guiding the construction of statistical analyses. In other words, it is up to clinically  
203 and scientifically informed disproportionality analyses, not statistics alone, to identify  
204 plausible directions of causality and the necessary follow-up studies.

205           Specifically, reverse causality (DAG B in Figure 1) could be anticipated by  
206 carefully considering which drugs are used to treat the condition investigated. For  
207 instance, one could run analyses only on reports that do not include drugs used to

208 treat communication disorders. Similarly, clinical expertise can identify whether  
209 underlying conditions are also likely to cause the adverse events of interest  
210 (Confounding by Indication, DAG C in Figure 1). This is the case of psychotic and  
211 affective disorders being associated with communicative impairments (e.g., flat  
212 prosody for both types of disorders, and semantic incoherence for psychotic  
213 disorders). A solution to this bias is to explicitly include the common cause in the  
214 model (“blocking the backdoor path” (Pearl, 2009)), for instance, by analyzing the  
215 populations separately: in our case, this implies separately analyzing individuals with  
216 affective disorders, individuals with psychotic disorders, and individuals without any  
217 neurologic medication in order to test whether patients with, e.g., affective disorders  
218 on vs. off a specific drug display higher rates of the adverse event of interest. By  
219 looking at reports for individuals not taking any neurologic medication, it is possible  
220 to exclude (and therefore correct for) psychiatric patients as well as other  
221 communication-impairing conditions such as anxiety, Parkinson’s disease, and  
222 dementia. This analysis is, of course, a first approximation: affective and psychotic  
223 disorders are complex conditions with very heterogeneous clinical profiles,  
224 comorbidities, and therapies. To move one step further, one could identify other  
225 underlying comorbid conditions likely to cause communicative impairments and  
226 produce a control analysis where all these conditions are excluded. Similarly, in the  
227 Confounding by Concomitant case (DAG D in Figure 1), one could identify drugs  
228 known to produce communicative impairments and exclude reports containing these  
229 drugs from the analysis. This also deals with what is known as “competition bias”  
230 (Raschi et al., 2018): known adverse drug reactions are easier to detect and  
231 therefore reported more frequently. Thus, established adverse drug reactions result

232 in stronger associations, which mask the less reported unexpected ones. When  
233 known signals are removed, new associations may become visible.

234 While these techniques provide information about potential mechanisms, they  
235 do not guarantee accurate causal inference. Nevertheless, they contribute to the  
236 collective construction of more accurate knowledge on the relationship between  
237 drugs and communicative impairments by providing hypotheses to be explored and  
238 assessed in future investigations.

## 239 **Methods**

### 240 Overview of the analyses

241 The general pipeline of the analysis is represented in **Figure 2**, the details of  
242 which are explained in the following paragraphs.

### 243 Definition of search terms

244 We relied on two information sources: SIDER for clinical trial reports of  
245 adverse drug reactions and FAERS for spontaneous post-marketing reports. Both  
246 sources employ a standardized hierarchical lexicon to code for adverse events, the  
247 Medical Dictionary for Regulatory Activities or MedDRA® (an international medical  
248 terminology developed under the auspices of the International Council for  
249 Harmonisation of Technical Requirements for Pharmaceuticals for Human Use –  
250 ICH). In MedDRA, the highest organization level is the System Organ Class (SOC,  
251 e.g., nervous system vs. vascular disorders), followed by the High-Level Group  
252 Terms (HLGTs, e.g., neuromuscular vs. neurological disorders), followed by High-  
253 Level Terms (HLTs, e.g., muscle tone abnormal vs. motor neuron disease) and  
254 Preferred Terms (PTs, e.g., hypertonia vs. hypotonia). Both SIDER and FAERS code  
255 their adverse events as preferred terms.

256           The MedDRA lexicon has some limitations that are important to acknowledge.  
257   First, the MedDRA does not always include the most adequate terms to report a  
258   given adverse event; therefore, some events are less likely to be reported or are  
259   reported relying on only partially relevant terms. Second, the same event may be  
260   reported using different MedDRA terms, often coded in different branches of the  
261   MedDRA dictionary. For instance, speech sound disorder is coded as a psychiatric  
262   event among “communication disorders and disturbances”, while dysphonia is coded  
263   as a respiratory event among “respiratory, thoracic and mediastinal disorders”. Third,  
264   and even more concerning is the limitation ensuing from the inconsistency between  
265   the MedDRA and different relevant conceptual frameworks to understand  
266   communicative impairments. The current study must rely on the MedDRA lexicon,  
267   since both its information sources - SIDER and FAERS - code their adverse events  
268   as MedDRA preferred terms. However, caution is needed in interpreting MedDRA  
269   terms in this study. The MedDRA has been developed to facilitate the identification  
270   of signs and symptoms - emerging as drug related adverse reactions – by a broad  
271   range of users with a diverse set of expertise: from clinical practitioners to patients  
272   and caregivers. Therefore, its terms do not easily map onto other very relevant  
273   frameworks, such as the categories of communication impairments as investigated  
274   within psychotic and affective disorders, and the nosological entities of the speech  
275   and language pathology community, built to systematize knowledge on commonly  
276   co-occurring signs and symptoms and their underlying mechanisms. For instance,  
277   while impairments in prosody are commonly considered a speech motor control  
278   issue in the domain of speech and language pathology, in the study of affective and  
279   psychotic disorders it is associated with flat and blunted affect, that is, with emotional

280 aspects of the conditions. This implies differences in how prosody-related  
281 impairments would be categorized.

282 In order to partially overcome these limitations and to tailor the categories to  
283 the question at hand, good pharmacovigilance practices rely on the so-called  
284 Standardized MedDRA Queries (SMQs), which are expert-validated search queries  
285 that aggregate many partially overlapping preferred terms across the MedDRA to  
286 identify and retrieve cases of interest. In the absence of an SMQ for communicative  
287 impairments, six clinical and domain experts (pharmacovigilance experts, speech-  
288 language pathologists, psychologists, and experts on voice markers of affective and  
289 psychotic disorders; see the list of co-authors) independently clustered the  
290 communicative PTs based on semantic overlapping, and disagreements were  
291 discussed among the team until resolved. The multidisciplinary team developed the  
292 clusters considering that diverse and not necessarily expert reporters may use  
293 multiple terms to identify the same communicative impairment. Additionally, we  
294 excluded from disproportionality analysis generic PTs (e.g., speech disorder), which  
295 often imply low specificity in the report and could in principle indicate any  
296 communicative impairment.

## 297 The FDA Adverse Event Reporting System (FAERS)

298 The United States Food and Drug Administration (FDA) Adverse Event  
299 Reporting System (FAERS) collects worldwide spontaneous reports of suspected  
300 adverse drug reactions and offers the highest accessibility to the public for  
301 customized analyses. Specifically, its raw quarterly data include demographic,  
302 therapeutic, and outcome details for each individual report. The reaction (adverse

303 event) and indication (why the drug was administered) fields are standardized using  
304 MedDRA preferred terms.

305 The entire FAERS - Quarterly Data (FDA, 2022) (January 2004 to June 2021)  
306 was downloaded and pre-processed to remove duplicate reports and standardize  
307 PTs and drug names. For the standardization of PTs, we used MedDRA 24.0. For  
308 the standardization of drug names, we used the WHO drug dictionary accessed in  
309 March 2020 and iteratively integrated to include newly marketed active ingredients.  
310 Furthermore, drug names were linked to their specific code from the Anatomical  
311 Therapeutic Chemical (ATC) hierarchical classification (2022 version) to allow group  
312 visualization of similar drugs. Because individual substances can have multiple  
313 codes related to distinct indications of use or administration routes, we selected only  
314 one code for each active ingredient using a semi-automatic prioritizing algorithm  
315 (Gaimari et al., 2022).

## 316 Exposure of interest

317 In order to identify medications associated with communicative impairments  
318 and deal with possible “common cause” biases (DAG C in Figure 1), we separately  
319 investigated three clinical populations: patients with a) affective, b) psychotic  
320 conditions, and c) without any neurologic medications (i.e., likely without any  
321 neuropsychiatric conditions, hereafter termed non-neuropsychiatric reports). To  
322 identify patients with psychotic and affective conditions we selected all reports that  
323 recorded, as a reason for using drugs, any PT (for example, ‘schizophrenia’)  
324 belonging to the HLGs for psychotic disorders (“schizophrenia and other psychotic  
325 disorders”) and affective disorders (“manic and bipolar mood disorders and  
326 disturbances” and “depressed mood disorders and disturbances”). To identify



327 patients without neuropsychiatric conditions, we selected all reports that did not  
328 include any neurologic drug (according to the ATC) nor any psychotic or affective  
329 preferred term. The results of the selection procedure are displayed in the  
330 Supplementary Material 1 – Section C – Figure S1.

331 Descriptive analyses were performed to characterize cases (displaying  
332 communicative impairments) vs. non-cases separately in the three populations of  
333 interest, with a particular focus on demographics, concomitants, co-reported events,  
334 and comorbidities (Supplementary Material 1 Section C). Differences between cases  
335 and non-cases may point to susceptibilities and potential biases not a priori  
336 acknowledged. For example, if we find that older people are more represented in  
337 cases than non-cases, this may point to a potential bias related to a higher frequency  
338 of speech disorders in the elderly.

### 339 Disproportionality analyses for drug-event association detection

340 Disproportionality analysis (the analysis of a reliably more frequent reporting  
341 of an adverse event in presence of a drug than in presence of any other drug, Figure  
342 2 – Step 1) was performed following good signal detection guidelines (Wisniewski et  
343 al., 2016). Using a contingency table 2x2, we calculated the Reporting Odds Ratio  
344 (ROR) whenever at least 10 cases of the event investigated co-occurred with the  
345 drug investigated. In fact, when few cases have been collected, the probability of  
346 detecting spurious associations is high. Considering a threshold of 10 cases allowed  
347 us to reduce this risk at the cost of missing some true associations for which not  
348 enough cases had yet been collected (e.g., for particularly novel drugs), and can be  
349 seen as an alternative to other conservative methods, such as the information  
350 component (Norén et al., 2013). The ROR was deemed significant when the lower

351 limit of its 95% confidence interval was greater than 1. In other words, we report a  
352 potential association when the adverse event is more likely to be reported together  
353 with the drug of interest than with any other drug but the one analyzed.

354 We performed a disproportionality analysis evaluating associations between  
355 drugs (from the ATC 2022 classification, excluding mineral supplements and drugs  
356 included in the 'Various' class) and communication-related adverse events (sub-  
357 clusters of overlapping terms as identified in **Table 1**). The analyses were run on all  
358 reports involving a) affective and b) psychotic disorders, and c) non-neuropsychiatric  
359 reports. To filter out likely spurious associations, results were subjected to Bonferroni  
360 correction.

### 361 The Side Effect Resource (SIDER)

362 The Side Effect Resource is a public database that grants free access to the  
363 information contained in the package inserts, that is, the official information on a drug  
364 and its uses, in particular its side effects, compiled and distributed by the drug  
365 manufacturers. Package inserts are text-mined, and the information retrieved  
366 is coded using the ATC classification for medications and the MedDRA classification  
367 for adverse events.

368 For each subquery of potential adverse reactions, we searched the  
369 specific preferred terms. We considered the identified medications as expected  
370 associations (Figure 2 – Step 2), which did not require further discussion of potential  
371 biases and causal mechanisms. The associations found in FAERS but not present in  
372 the SIDER were considered unexpected and were further assessed for potential  
373 causal confounding (Figure 2 – Step 3).

## 374 Robustness Analyses

375           Drugs unexpectedly associated with the sub-queries investigated were  
376 stratified according to expected biases (Figure 2 – Step 4) through clinical  
377 reasoning and according to the causal inference framework discussed in the  
378 introduction (paragraphs 1.3 and 1.4). We accordingly separated the associations  
379 into uncontroversial ones (plausible adverse reactions, Figure 1, DAG A, for which  
380 no specific confounder was expected), potential reverse causality (Figure 1,  
381 DAG B), potential confounding by indication (Figure 1, DAG C), and by concomitant  
382 (Figure 1, DAG D). Robustness analyses adjusted the estimates for  
383 possible confounders (Figure 2 – Step 5): excluding reports with the communicative  
384 impairment among indications or restricting the investigation to a specific indication,  
385 to account for reverse causality bias (DAG B; Robustness Analysis 1); excluding  
386 reports with pathologies that may be responsible for indication bias (DAG C;  
387 Robustness Analysis 2), at least for drugs that are approved for multiple indications;  
388 excluding reports with the drug responsible for the ambiguity to account for the  
389 concomitant bias (DAG D; Robustness Analysis 3). The procedure applied is  
390 documented in Supplementary Material 1 – Section D.

## 391 Aggregating Results

392           The expected adverse drug reactions from the SIDER and robust unexpected  
393 associations from the FAERS were aggregated in a list per each main cluster of  
394 overlapping PTs, Figure 2 – Step 6. To provide a detailed overview of the results, we  
395 visualized each list as a table showing expected and previously unexpected adverse  
396 reactions organized according to the ATC hierarchical classification  
397 (see Supplementary Material 1 – Section D).

398 To provide a more general overview of the drug classes that should be  
399 considered for the analysis of communication-related markers, we built a heat map  
400 showing the associations at the third level of the ATC classification (e.g.,  
401 antipsychotics, antihistamines, and antidepressants; see the public repository (M.  
402 Fusaroli & Fusaroli, 2021) for a collated heatmap at the level of single active  
403 ingredients).

## 404 Results

### 405 MedDRA query for case retrieval

406 We defined nine clusters of overlapping MedDRA PTs referring to communicative  
407 impairments. For simplicity, we named the clusters with reference to the semantic  
408 overlap and specific concerns (communicative impairments in affective and  
409 psychotic disorders) that guided the aggregation: related to 1) dysphonia, 2) speech  
410 motor control disorders, 3) prosody, 4) aphasia, 5) tachyphrenia, 6) bradyphrenia, 7)  
411 abnormal reasoning, 8) stereotypy, and 9) incoherence (see Table 1). Sixteen of the  
412 communicative PTs were excluded from clustering and the subsequent analyses. It  
413 is important to note that the clusters might not be entirely coherent with current uses  
414 of the terms in the speech and language pathology community, but they were the  
415 result of an interdisciplinary consensus, and they will be discussed and clarified  
416 where they could generate misunderstandings.

### 417 Populations of interest

418 We selected three populations of interest: 302,000 reports involving affective  
419 disorders, 11,631 psychotic disorders, and 7,703,183 non-neuropsychiatric  
420 disorders. A detailed presentation of the number of cases (reports with

421 communication-related adverse events) and non-cases is presented in the  
422 Supplementary Material 1 – Section C Figures S1-S5 and Table S2.

### 423 Expected and Unexpected Solid Associations

424 Disproportionality results and effect size for each cluster and each population are  
425 reported in the Supplementary Material 2. We detected both expected – according to  
426 the SIDER - and unexpected drug associations and performed robustness analyses  
427 on the latter ones. The result was a list of 291 expected and 91 unexpected potential  
428 confounding medications. Emerging results are shown in Supplementary Material 1 -  
429 Section C (Tables S3-S9, Figure S6). No association was found for the prosody and  
430 abnormal reasoning clusters.

431 We detected 72 drug classes (ATC third level) associated with a  
432 disproportional reporting of the dysphonia cluster: 53 were already expected based  
433 on the SIDER, 10 classes included both drugs already reported in the SIDER and  
434 unexpected drugs (integrated classes) and 9 were entirely unexpected. Restricting to  
435 strong signals (i.e., disproportions significant after the Bonferroni correction) in the  
436 non-neuropsychiatric population, the highest number of cases involved inhalants –  
437 fluticasone (4669 cases, ROR = 10.48, 95% CIs = [10.14-10.81]), salmeterol (3099,  
438 12.16 [11.71-12.63]), and salbutamol (2434, 5.52 [5.29-5.76]), while the highest  
439 lower limits of the 95%CI of the ROR concerned two VEGFR-inhibitors –regorafenib  
440 (530, 22.25 [20.29-24.35]) and axitinib (437, 14.27 [12.92-15.37]) and salmeterol.  
441 The many anticholinergic drugs already present in the SIDER were integrated with  
442 unexpected signals for umeclidinium (an inhaled bronchodilators), rupatadine and  
443 fexofenadine (antihistamines). Among the robustness analyses implemented, we  
444 accounted for reverse causality (DAG B: botulinum toxin excluding its use for

445 spasmodic dysphonia(Faham et al., 2021)), confounding by indications (DAG C:  
446 antihistamines restricted to urticaria, to exclude the confound due to asthma) and  
447 concomitants (DAG D: cardiovascular agents excluding angiotensin-converting  
448 enzyme inhibitors; beta agonists excluding inhalants).

449 We detected 37 drug classes associated with a disproportional reporting of  
450 the speech motor control cluster (17 expected, 10 integrated, 10 unexpected). The  
451 most numerous cases concerned immunomodulators used in multiple sclerosis –  
452 natalizumab (770, 4.48 [4.16-4.82]) and interferon beta-1a (674, 3.62 [3.34-3.91]) –  
453 and a selective calcium channel blocker – amlodipine (376, 2.05 [1.84-2.27]). Drugs  
454 with the highest lower limit were anti-infectives: vidarabine (20, 71.42 [42.66-  
455 113.63]), valaciclovir (334, 12.14 [10.84-13.55]) and metronidazole (309, 9.48 [8.44-  
456 10.63]).

457 A total of 51 drug classes were associated with the aphasia cluster (19  
458 expected, 10 integrated, 22 unexpected), with the most numerous being natalizumab  
459 (872, 5.54 [5.16-5.94]), interferon beta-1a (643, 3.71 [3.42-4.02]), and levothyroxine  
460 (327, 1.57 [1.4-1.75]), and the highest disproportionalities being with antineoplastic  
461 such as CAR-T engineered cells used to treat hematologic neoplasia –axicabtagene  
462 ciloleucel (114, 43.68 [35.78-52.8]) and tisagenlecleucel-t (58, 24.5 [18.52-31.84])–  
463 and avapritinib (20, 18 [10.33-26.44]).

464 Concerning the stereotypy cluster, we did not find any unexpected signal and  
465 only four expected drug classes: antineoplastic (ifosfamide), antiepileptic  
466 (topiramate), antiepileptic (phenelzine and bupropion), and contrast agents  
467 (iopamidol). The only strong signal was with interferon beta-1a in non-  
468 neuropsychiatric patients (20, 6.12 [3.65-9.73]).

469 A total of 12 drug classes were associated with the tachyphrenia cluster (4  
470 unexpected, 2 integrated, 6 expected). We observed associations based on only few  
471 cases, the greatest being clarithromycin (49, 22.38 [16.43-29.8]), levothyroxine (47,  
472 2.29 [1.67-3.07]) and ivermectin (40, 99.9 [70.83-137.18]), with the highest  
473 disproportionalities for ivermectin, clarithromycin and niraparib (11, 10.54 [5.24-  
474 18.94]).

475 A total of 10 drug classes were associated with the bradyphrenia cluster (2  
476 unexpected, 2 integrated, 6 expected), the most common drugs being natalizumab  
477 (105, 4.65 [3.77-5.67]), levothyroxine (85, 2.97 [2.36-3.7]) and interferon beta-1a (65,  
478 2.6 [2-3.34]), the strongest signals being with lorcaserin (17, 40.85 [23.67-65.71]),  
479 finasteride (33, 11.9 [8.16-16.79]) and natalizumab.

480 Finally, 44 drug classes were associated with the incoherence cluster (34  
481 expected, 4 integrated, 6 unexpected), the more numerous substances being  
482 levothyroxine (237, 1.9 [1.67-2.17]), interferon beta-1a (213, 1.98 [1.72-2.27]) and  
483 montelukast (200, 5.58 [4.82-6.43]), and the highest disproportionalities being those  
484 with anti-infectives –mefloquine (33, 36.26 [24.8-51.28]), zanamivir (14, 11.95 [6.51-  
485 20.13]) and oseltamivir (62, 6.47 [4.95-8.31]).

486

487

## Discussion

### Overview

489 Given the increased focus on communication-related markers of affective and  
490 psychotic disorders, there is an increased need for a careful overview of how  
491 medications could act as confounders. The current study rigorously combined  
492 evidence from drug package inserts with post-marketing disproportionality analyses

493 and relied on causal inference techniques to account for potential biases, in order to  
494 provide a first attempt at such an overview.

495 In the following subsections, we discuss how to interpret and use these  
496 findings and methods in the broader context of digital phenotyping trying to identify  
497 markers of neuropsychiatric conditions: discussing expected and unexpected  
498 potential adverse reactions as they relate to the specific context of communication-  
499 related markers of psychotic and affective disorders; presenting the limitations and  
500 possibilities of our approach; and discussing possible realistic uses of the list in  
501 future research.

## 502 Known and unexpected adverse reactions

503 The final list of potential confounding drugs for communication-related  
504 markers encompasses both expected (i.e., described in the package insert) and  
505 unexpected associations. Some of the expected associations are already discussed  
506 in the literature on communication-related markers. For example, the effects of  
507 antipsychotics and antidepressants have been directly investigated when evaluating  
508 communication-related markers (Cohen et al., 2017; Cummins et al., 2015; de Boer  
509 et al., 2020; Püschel et al., 1998; Sinha et al., 2015). However, even these expected  
510 associations are not routinely considered in the actual analysis of communication-  
511 related markers of psychotic disorders (Parola et al., 2020), and when they are, the  
512 results are inconclusive (Parola, Lin, et al., 2022; Parola, Simonsen, et al., 2022).

513 In other cases, we found unexpected associations with drugs from already  
514 known classes (integrated findings, that is, drugs from the same class were already  
515 known to associate with the adverse reaction). For instance, clonazepam (an  
516 antiepileptic, also used to treat anxiety) being associated with the aphasia cluster



517 and for antineoplastic agents (mainly VEGFR-inhibitors) with the dysphonia cluster.  
518 Some drugs' package inserts, in fact, did not list all the possible preferred terms that  
519 could be used to describe their side effects. This led to the classification of certain  
520 expected drug reactions as unexpected (e.g., the package inserts for haloperidol  
521 only mentioned motor control disorders, but not speech motor control disorders),  
522 even if the scientific literature or clinical practitioners may already be aware of them.

523 Other associations are more unexpected. Medications used to treat cancer,  
524 such as plant alkaloids, cytotoxic antibiotics, protein kinase inhibitors, and  
525 monoclonal antibodies, emerge as potential causes of aphasia, which are not  
526 reported in the SIDER database. Crucially, since there is at least some evidence of  
527 increased cancer risk in schizophrenia (Nordentoft et al., 2021), we could expect a  
528 more common use of these drugs in patients with schizophrenia than in controls.  
529 Therefore, the adverse reaction could influence how well a predictive model could  
530 detect psychotic disorders from speech or language patterns, at least in complex  
531 machine learning models. Nevertheless, these drugs have never been mentioned -  
532 to our knowledge - in previous studies of communication-related markers as possible  
533 confounders.

### 534 Drug-induced communicative impairment mechanisms

535 We contextualized the drugs identified as possible confounders for  
536 communication-related markers according to their plausible mechanism of action  
537 (see **Figure 3**). Indeed, biological plausibility is one element of credibility for  
538 hypotheses emerging from disproportionality analyses. Furthermore, understanding  
539 the mechanism underlying drug-induced communication atypicalities may allow to  
540 identify other plausible involved drugs not detected in our study (e.g., because of

541 unaccounted for biases, or because still not on the market). Finally, the knowledge of  
542 exactly how communication-related markers are affected by each drug may be  
543 included in machine learning algorithm to provide more reliable predictions.

544 The role of drugs in inducing phonatory impairment, often reported as  
545 hoarseness, is already consolidated for multiple drugs (see **Table S3**). The primary  
546 responsible - in terms of numbers - is plausibly **anticholinergic toxicity** because of  
547 xerostomia and larynx desiccation (antimuscarinic inhaled bronchodilators,  
548 spasmolytics, drugs for overactive bladder, muscle relaxants, antidepressants,  
549 antipsychotics, antihistamines) (Haft et al., 2015). Notably, we observed a signal for  
550 second and third generation antihistamines which, trespassing less the blood brain  
551 barrier, preserve from central anticholinergic toxicity (mainly sedation) but may  
552 nonetheless exert their peripheral effect on salivary glands. The drying effect of  
553 diuretics, secondary to hypovolemia, is controversial (Schwartz et al., 2009). Instead,  
554 drug-related **laryngeal irritation** is an established common condition, whether  
555 because of inhaled drugs (corticosteroids – especially dry powders (Galván &  
556 Guarderas, 2012) – beta-agonists and mast-cell stabilizers), drugs inducing cough  
557 such as angiotensin converting enzyme inhibitors (Bangalore et al., 2010), or  
558 improperly taken bisphosphonates (Hanna et al., 2012). In fact, for inhalants and  
559 other respiratory drugs (xanthines, leukotriene receptor antagonists, respiratory  
560 monoclonal antibodies), it is often difficult to differentiate between the role of the drug  
561 and the underlying disease.

562 Drug-induced **organic lesions of vocal cords** may also be responsible for  
563 dysphonia, as in the case of hemorrhages induced by anti-thrombotics, anti-  
564 inflammatories, and 5-phosphodiesterase inhibitors (Stachler et al., 2018), reversible  
565 nodules due to excessive granulation response induced by acitretin and isotretinoin

566 (Busso & Serrano, 2005; Kim et al., 2006), or necrosis due to the antiangiogenic  
567 activity of VEGFR-inhibitors (Kudo et al., 2018; Melo et al., 2019; Motzer et al., 2013;  
568 Saavedra et al., 2014; Sulibhavi et al., 2020; Wen et al., 2018). Sex hormones may  
569 also be involved (Zamponi et al., 2021), as for androgens and antigonadotropins  
570 inducing vocal cords thickening and voice deepening through androgen receptors on  
571 the larynx (Chadwick et al., 2021). Furthermore, antineoplastics and  
572 immunomodulating drugs are also known to be associated with dysphonia, plausibly  
573 due both to the cytotoxic (Berretta et al., 2004) and immunomodulating role of the  
574 drug (Benfaremo et al., 2018; Bruno et al., 2021), to the disease (Gavrila et al.,  
575 2015), and to concomitant radiotherapy (Villari & Courey, 2015).

576 Finally, an impairment in phonation may be due to extrapyramidal **dystonia**  
577 (mainly antipsychotics, but also dopamine antagonist antiemetics such as  
578 metoclopramide, that was subjected to an FDA black box warning for dyskinesia,  
579 with involuntary movements of the tongue) or to botulinum-related **flaccid paralysis**  
580 (a black box warning for systemic toxicity was added to the package insert on 2009).

581 Other drug classes expected based on SIDER are insulins, 5HT3 antagonist  
582 antiemetics, antimycotics, antivirals, dopamine agonists, cholinergic drugs, cough  
583 preparations, antiepileptics, analgesics and anesthetics, anxiolytics and sedatives,  
584 and cardiovascular drugs. These drug are themselves not totally free of confounding,  
585 such as confounding by indication (DAG C: diabetes (Hamdan et al., 2013), cough,  
586 and vomit) and reverse causality (DAG B: proton pump inhibitors – for dysphonia  
587 supposedly due to laryngo-esophageal reflux (Lechien et al., 2017; Ruiz et al., 2014)  
588 – and antibiotics – for dysphonia supposedly due to respiratory infections (Stachler  
589 et al., 2018)).

590 The role of drugs in inducing speech motor control impairment is already  
591 consolidated for dopamine antagonists-related acute dystonia and tardive dyskinesia  
592 (antipsychotics), agents inducing sedation and reduced speech motor control  
593 (anxiolytics, antiepileptics, opioids, antidepressants, anticholinergic drugs, muscle  
594 relaxants), neurotoxic drugs (anti-infective, antineoplastic and immunomodulator  
595 agents), dopamine agonists (Craig-McQuaide et al., 2014), and drugs interacting  
596 with catecholaminergic and GABAergic pathways (Ekhart et al., 2021). We also  
597 observed an association with antineoplastics and immunomodulators – plausibly due  
598 to their neurotoxicity – and with cardiovascular agents and hormones. Interestingly,  
599 the signal for antithrombotic medications persisted when excluding ischemic and  
600 unspecified stroke cases. Even if we cannot exclude reverse causality and indication  
601 bias, this signal may point to the possibility of drug-induced cerebral hemorrhages.

602 Multiple cases of iatrogenic aphasia have been reported in the last decade  
603 (Rizwan et al., 2021), often concerning reversible conditions induced by  
604 immunomodulators, chemotherapy and fluoroquinolones-related neurotoxicity (Belin  
605 et al., 2020; Bennett et al., 2019; Carl et al., 2015; Higa et al., 1995; Patel et al.,  
606 2015). A similar toxicity may also manifest because of the increased permeability of  
607 the blood brain barrier due to contrast media, potentially allowing endogenous and  
608 exogenous neurotoxins to reach the central nervous system. Dopamine antagonism  
609 (Chien et al., 2017), shared by antipsychotics and the propulsive domperidone, may  
610 also be responsible for aphasia, as well as antithrombotic-related hemorrhages.  
611 Bradyphrenia and tachyphrenia may also be the manifestation of neurotoxicity, and  
612 of sedation (e.g., antiepileptics, pramipexole, antipsychotics, lithium,  
613 benzodiazepines, antidepressants, antihistamines, cannabinoids) and excitation  
614 (levothyroxine, psychostimulants), respectively.

## 615 Limitations and future directions

### 616 Formalized query

617           In the attempt to retrieve cases of interest in the FAERS, we found an often-  
618 ambiguous lexicon covering communicative impairments. The current study explicitly  
619 formalized a MedDRA query to retrieve communicative impairments relevant to  
620 affective and psychotic disorders more systematically. This formalized query is a  
621 necessary step to focus the attention and to create a common framework for  
622 disproportionality analyses on these impairments.

623           The current query presents some limitations. First, one might more closely  
624 investigate how physicians describe and report these impairments. For example,  
625 common terms used by physicians to report dysphonia are acute laryngitis,  
626 nonspecific dysphonia, benign vocal fold lesions, and chronic laryngitis (Stachler et  
627 al., 2018), and for retrieving antipsychotic-related dysarthria cases one may search  
628 also for extrapyramidal syndrome and laryngospasm. More work is needed to cover  
629 these labels and validate the results of searches that integrate them. Second,  
630 perhaps more crucially, we observed a high proportion of communication-related  
631 FAERS cases submitted by the general public. This suggests that communicative  
632 adverse events might be at the same time underplayed by medical practitioners, and  
633 of crucial importance to patients, caregivers, and families. In fact, we observed that  
634 patients with communicative impairments tend to specify the resulting disability more  
635 frequently in their reports than patients with other adverse events but the same  
636 underlying condition. Third, during the definition of the query, we found several  
637 inconsistencies between the clusters of relevant MedDRA terms and terminological

638 practices in the speech and language pathology community, which could create  
639 unnecessary confusion.

640 One could also question whether FAERS' and SIDER information is  
641 sufficiently sensitive to the kind of properties analyzed in the search for  
642 communication-related markers. For example, minor acoustic atypicalities such as  
643 increased jitter – low-level irregularities in voice pitch, a commonly used acoustic  
644 measure in predictive, machine learning algorithms for affective and psychotic  
645 disorders (Cummins et al., 2015; Parola et al., 2020) as well as for Parkinson's  
646 disease (Tsanas & Arora, 2021) – might not be perceived, or at least not perceived  
647 as enough of an issue, by patients and clinicians to be reported and precisely  
648 labeled. This suggests that a closer collaboration of patients and practitioners –  
649 crucially including speech and language pathology and communicative markers  
650 experts – in developing a common and easy to use terminology and clear definitions  
651 for communicative impairments would provide a substantial improvement for the  
652 MedDRA lexicon.

653 Nevertheless, the construction of an initial query enables initial explorations of  
654 medication-based confounders and facilitates proposals, thus representing an  
655 important step in the development of a useful Standardized MedDRA Query (SMQ).

## 656 Causal inference

657 Although still uncommon in disproportionality analyses, formalized causal  
658 inference, and the use of DAGs, in particular, are a promising endeavor  
659 (Cunningham, 2021; Pearl, 2009). These tools provide a standardized framework for  
660 the formalization, visualization, and communication of confounding. These tools also  
661 provide structured and more reproducible procedures to account for at least some of  
662 the biases when designing analyses (Pearl, 2009).

663 We have built four relatively simple DAGs of the mechanisms underlying  
664 observed drug event observations. Thus, we have tried to identify the most  
665 problematic biases for our questions and accordingly adjusted our analyses and  
666 interpretation. However, it is important to note that many biases could not be fixed  
667 and that the characteristics of the reporting (often incomplete and unverified)  
668 complicate attempts at causal inference. For example, proton pump inhibitors are  
669 used to treat or prevent gastroesophageal reflux, a condition that may also affect the  
670 larynx and vocal cords and result in laryngo-esophageal reflux disease and  
671 dysphonia (Lechien et al., 2017). Therefore the causal direction (PPI to dysphonia,  
672 or reflux to both PPI and dysphonia) cannot be easily identified. Further, our broad  
673 focus did not permit us to delve into the richness of spontaneous reports (e.g.,  
674 information on concomitants, therapy regimen, co-occurring events) and to map  
675 more complex scenarios (e.g., variables affecting at the same time the use of the  
676 drug, the incidence of the adverse event, and the reporting of it). For example,  
677 botulinum toxin has been referred to as a potential cause and treatment for  
678 spasmodic dysphonia but may also temporarily cause dysphonia through muscle  
679 weakening. In addition, biases, such as notoriety bias, and masking bias, adjustment  
680 for the Weber effect (Raschi et al., 2018), are beyond the scope of this study but  
681 should be considered when investigating specific drugs more closely. Further,  
682 because of the many biases of spontaneous reporting, the comparison of the safety  
683 profile of different drugs on the basis of disproportionality alone tends to be  
684 unreliable and is in general not recommended (Mouffak et al., 2021).

#### 685 Integrating additional sources

686 The main objective of spontaneous reporting systems is to collect useful data  
687 to identify unexpected associations between a drug and an adverse event in a timely

688 and cost-effective manner. This identification enables early intervention and  
689 therefore limits the costs of drug-related harm. To effectively target currently not  
690 known safety issues, it is extremely important to integrate already acquired  
691 knowledge, which may come from the literature, or from regulatory sources -  
692 primarily package inserts (FDA) and Summaries of product characteristics (EMA).

693 Databases that store this information in an easily accessible way are a  
694 promising tool for large-scale analyses because reading and coding each individual  
695 package insert would be extremely time consuming. The SIDER uses a natural  
696 language processing algorithm to extract the information from regulatory sources  
697 and has not been updated since 2016 (Kuhn et al., 2016), therefore, it plausibly  
698 contains errors and outdated information. Furthermore, it may contain terms linked  
699 but not coincident with the investigated events (as in the case of haloperidol), and  
700 therefore our automated process may lack some expected reactions.

701 A worldwide database in which data for each marketed drug is compiled and  
702 regularly updated by the marketing authorization holder and stored in an accessible  
703 way would enrich both regulatory activities and disproportionality analyses. In the  
704 meantime, the use of the SIDER or similar databases may help in large-scale  
705 analyses to reduce the risk of classifying already known reactions as unexpected  
706 signals.

707 We cannot be sure whether some of the unexpected associations have  
708 already appeared as notes in clinical trials (but not reported in the package insert) or  
709 in subsequent scientific literature. Future work should attempt to integrate these  
710 additional sources of information. However, independent of the novelty, our list  
711 aggregates large amounts of otherwise dispersed information in an easier to consult  
712 format.



713 Future work could integrate additional sources of information, both as related  
714 to known associations (e.g., scientific literature) and additional clinical data (e.g.,  
715 health records), to provide a more comprehensive overview. Further, different  
716 sources could be weighted according to the degree of evidence available (e.g., via  
717 Bayesian analysis).

#### 718 Large-scale analyses

719 Traditional disproportionality analyses focus on at most a handful of drugs  
720 and/or adverse events (Aiello et al., 2021; Raschi et al., 2020). Thus, they can  
721 provide a fine-grained analysis of potential confounders, including a nuanced  
722 analysis of how sociodemographic variables might affect drug prescription and  
723 adverse reactions (Hoekstra et al., 2021).

724 Large-scale analyses require a broader overview, which cannot match the  
725 same level of detail and discussion. The strategies we implemented to  
726 simultaneously assess large sets of adverse events and drugs may help design  
727 future large-scale analyses. These strategies range from correction for multiple  
728 testing and automatic integration with regulatory databases, to an attempt to  
729 formalize possible underlying causal mechanisms and the use of a priori expected  
730 biases to implement robustness analyses. Large-scale analyses, however, provide  
731 only an initial perspective and must be complemented with more detailed studies of  
732 specific associations and their confounds.

#### 733 How should this list be used?

734 We advocate for the list of drug confounders (Figure 3 and Supplementary  
735 Material 1 – Section D – Table S10)– whether as a cause of communicative  
736 atypicality or as a proxy of an underlying susceptibility – to be used in future studies

737 of communication-related behavioral markers by either including the presence of a  
738 medication as a covariate, removing participants who take medication, or interpreting  
739 results and study limitations as a function of which medications were taken. As  
740 observed in multiple reviews, most studies of such markers involve small sample  
741 sizes (R. Fusaroli et al., 2017; Parola et al., 2020; Weed & Fusaroli, 2020). Such  
742 studies would be at a loss trying to adjust for such a large number of medications  
743 and would lack reliable evidence related to all but the most commonly used ones  
744 (Rocca & Yarkoni, 2021; Westfall & Yarkoni, 2016). Although a single study may still  
745 check the list to identify likely cautions (e.g., much higher use of drug x in the target  
746 population than in the controls), the real potential lies in the cumulative aggregation  
747 of this information across studies. The key is to promote transparency of reporting  
748 and record medications used by participants in individual studies, which would allow  
749 future mega-analyses (R. Fusaroli et al., 2022) (aggregating datasets across studies  
750 preserving individual-level data) to directly assess the impact of a large variety of  
751 relevant medications.

752 Accounting for confounders is also important in machine learning studies.  
753 Current reviews and perspectives on the study of communication-related behavioral  
754 markers advocate the collection of larger and more diverse samples and the use of  
755 state-of-the-art machine learning techniques, such as deep learning (Parola, Lin, et  
756 al., 2022; Parola, Simonsen, et al., 2022; Rybner et al., 2022). In these contexts, the  
757 algorithms can detect even the presence of weak confounding if it improves  
758 prediction. In other words, many machine learning models are likely to recognize  
759 small differences between groups they try to classify. If these differences are due to  
760 higher levels of medication being used and not due to the target disorder, the models  
761 may not generalize well to other samples of the disorder where the medication use is

762 different, which is common when changing countries and sociodemographic settings.  
763 Accordingly, a deeper understanding of the confounders and mechanisms at work is  
764 a key component also for more data-driven machine learning approaches, for  
765 instance, to guide bias assessment or even to identify more rigorous pipelines (e.g.,  
766 presenting medication-balanced validation sets).

767 Finally, this list may also help identify more general hypothesized  
768 mechanisms underlying adverse events beyond a specific drug. Pharmaco-  
769 surveillance can thus act not only as a guide for precautionary regulatory action, but  
770 also as a hypothesis generation tool for scientific research, which could lead to  
771 follow-up studies involving, e.g., electronic health records (to assess adverse events  
772 before and after drug administration), experimental setups, and clinical studies. For  
773 instance, a more thorough investigation of the association between domperidone  
774 and aphasia would be of particular interest, given the biological plausibility (i.e., its  
775 activity as a dopamine antagonist) and the existence of conditions that increase the  
776 blood-brain barrier permeability. This might lead to more generalizable predictions  
777 regarding confounding drugs and an increased understanding of the communicative  
778 features of the disorders over time.

## 779 Applications of the methods to other neuropsychiatric conditions

780 In the current study, we have focused on affective and psychotic disorders  
781 since previous research explicitly called for better investigation of medication-related  
782 confounders in identifying communication markers for these populations (Cummins  
783 et al., 2015; Low et al., 2020; Parola et al., 2020). However, with proper  
784 consideration, the list could be easily extended when assessing communication-  
785 related behavioral markers for other conditions such as neurodevelopmental (e.g.,

786 autistic spectrum disorder) and neurological (e.g., Parkinson's disease) disorders. In  
787 particular, for Parkinson's disease, good practices to account for med-on and med-  
788 off levodopa state already exist (e.g., Im et al., 2019; Thies et al., 2021).

## 789 Conclusions

790 Motivated by the increasing interest in communication-related behavioral  
791 markers of affective and psychotic disorders, we set out to investigate the potential  
792 role of medications in affecting communication-related markers of these disorders.  
793 We extracted the drugs already expected to cause communicative impairments from  
794 the SIDER. This paved the way for a pharmacovigilance analysis of a larger set of  
795 communication-related adverse events and drugs, controlling for prominent biases.

796 We identified a list of medications to be accounted for in future studies on  
797 communication and biobehavioral markers of affective and psychotic disorders.  
798 These studies should take into account: drugs irritating vocal cords and the larynx  
799 (inhalants, bisphosphonates, angiotensin-converting enzyme inhibitors); drugs  
800 inducing laryngeal desiccation (anticholinergics, diuretics); drugs impairing speech  
801 motor control (anxiolytics, antiepileptics, opioids, antidepressants, anticholinergics,  
802 myorelaxants, antipsychotics, antiemetics), or temporarily paralyzing vocal cords  
803 (botulinum toxin); drugs inducing laryngeal hypertrophy (androgens,  
804 antigonadotropins) or the development of nodules on vocal cords (retinoids); drugs  
805 potentially inducing necrosis (VEGFR-inhibitors) or hemorrhages in the vocal cords  
806 (antithrombotics, nonsteroidal anti-inflammatories, PDE5-inhibitors); sedatives  
807 (anxiolytics, antiepileptics, antidepressants, hypnotics, antihistamines,  
808 cannabinoids); stimulants (psychostimulants, thyroid hormones, pramipexole); drugs  
809 interacting with catecholaminergic and GABAergic neurotransmitters; neurotoxic

810 drugs (antiinfectives, antineoplastics, immunomodulators, contrast media,  
811 antithrombotics).

812 The work showcases methodological innovations to facilitate large-scale  
813 disproportionality analyses and identifies current shortcomings, along with discussing  
814 potential causal and pathogenetic mechanisms. In particular, the existing lexicon to  
815 identify communicative adverse events is ambiguous and not well defined, perhaps  
816 due to an underappreciation of the perspectives of patients and lack of integration of  
817 experts in speech and language pathology and in communicative impairments. We  
818 advocate for future work on this.

819 Drugs that confound the effect between communication-related behavioral  
820 markers and psychiatric disorders are abundant. There should be concern not only  
821 for confounding drugs and comorbidities, but also non-medical substances and  
822 habits (e.g., smoking, vocal use). Here, we provide a tool for learning about and  
823 potentially adjusting for the confounders to improve digital phenotyping research.

824 Declarations

825 **Funding:** none

826 **Conflicts of interest/Competing interests:** RF has been a paid consultant for F.  
827 Hoffmann - La Roche.

828 **Ethics:** Anonymized data were collected from a publicly available database and did  
829 not require ethics committee approval.

830 **Authors' contributions:** MF, AS, and RF conceived the research project. MF, SB,  
831 AS, DML, AP, and RF defined the query for case retrieval. MF designed and  
832 executed the statistical analysis. MF, ER, EP, and RF reviewed and critiqued the  
833 statistical analysis. All the authors contributed to the interpretation of data. Regarding  
834 manuscript preparation, MF and RF executed the writing of the first draft and all the  
835 authors contributed to the review and critique. All authors approved the final version.

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840 registered by ICH.

841 **Data availability statement:** The pharmacovigilance data are freely accessible on  
842 the FDA website: <https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>  
843 [FAERS.html](https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html)

844 **Code access:** The code used is available upon request.

## **BIBLIOGRAPHY**

### **Supplementary Material**

Supplementary Material 1 includes an overview of the studies assessing the effect of medication on speech patterns in schizophrenia (Section A), the MedDRA Query developed for the retrieval of communication atypicalities (Section B), the features of the population investigated (Section C) and the summary of the results of the disproportionality analysis (Section D).

Supplementary Material 2 stores all the results of the disproportionality analysis, including the effect sizes.

**Figure 1 common causal mechanisms underlying drug adverse event associations.**

The four diagrams (A-D) represent four possible mechanisms which can all give rise to the observed association (in the center). The diagrams are direct acyclic graphs (DAGs), that is, graphs in which the nodes (ellipses) are the observable phenomena, and the arrows are the causal connections (which can only be acyclical, that is, go one direction and not form loops). **DAG A** represents the case in which the event is an actual Adverse Reaction caused by the administration of the drug of interest. **DAG B** represents a case of Reverse Causality, in which the drug is administered to treat the adverse event but is incorrectly reported. **DAG C** represents a case of Confounding by Indication, in which the underlying condition that justifies the use of the drug also more frequently induces the adverse event. **DAG D** represents a case of Confounding by Concomitant, in which the adverse event is a reaction to a co-administered drug (administered for the same condition or a related comorbidity).

**Figure 2 - Analysis pipeline.** Each step of the analysis is represented as a block and arrows indicate the flow of data from one step to the other. Descriptions of each step are provided in text.

**Figure 3 – Summary of drug-related communicative atypicalities’ plausible mechanisms.** Created with BioRender.com.



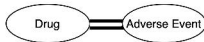
**Table 1 – MedDRA Query** for the retrieval of communicative atypicalities reports. We identified multiple sub-queries including semantically overlapping MedDRA Preferred Terms. The clusters were obtained on the basis of semantic overlapping, and therefore on the possibility that the reporters may have used interchangeably different terms, rather than with a reference to existing speech and language pathologies.

Cluster	MedDRA Preferred Terms		
<b>Cluster 1 (dysphonia-related)</b>	Dysphonia Dysphonia psychogenic Muscle tension dysphonia	Spasmodic dysphonia Aphonia Aphonia psychogenic	Phonastenia Stridor
<b>Cluster 2 (speech motor control-related)</b>	Dysarthria Dyslalia	Dysphemia	
<b>Cluster 3 (prosody-related)</b>	Aprosody Dysprosody		
<b>Cluster 4 (aphasia-related)</b>	Aphasia Primary progressive aphasia		
<b>Cluster 5 (tachyphrenia-related)</b>	Logorrhea Pressure of speech	Flight of ideas Tachyphrenia	
<b>Cluster 6 (bradyphrenia-related)</b>	Poverty of speech Bradyphrenia	Lack of spontaneous speech Poverty of thought content	Taciturnity Thought blocking
<b>Cluster 7 (abnormal reasoning-related)</b>	Ideas of reference Illogical thinking	Impaired reasoning Magical thinking	Paralogism
<b>Cluster 8 (stereotypy-related)</b>	Coprolalia Echolalia	Perseveration Repetitive speech	Verbigeration
<b>Cluster 9 (incoherence-related)</b>	Disorganized speech Incoherent Clang associations	Derailment Loose associations Tangentiality	Thinking abnormal
<b>Other terms excluded from clusters</b>	Pedantic speech Intellectualization Morbid thoughts Pathological doubt Intrusive thoughts Circumstantiality	Speech disorder developmental Mutism Speech disorder Cognitive linguistic disorder	Social communication disorder Language disorder Speech sound disorder Slow speech Confabulation

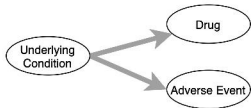
**DAG A: Adverse Drug Reaction**



**DAG B: Reverse Causality**



**DAG C: Confounding by Indication**



**DAG D: Confounding by Concomitant**

