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Incidence of Drug-Induced Delirium During Treatment With Antidepressants or Antipsychotics: A Drug Surveillance Report of German-Speaking Countries Between 1993 and 2016

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Abstract

Objectives: Successful treatment of delirium depends on the detection of the reversible contributors. Drugs with delirogenic properties are the most prevalent reversible cause of delirium.
Methods: This observational study is based on data from Arzneimittelsicherheit in der Psychiatrie, a multicenter drug surveillance program in German-speaking countries recording severe adverse drug reactions (ADRs) in psychiatric inpatients. The present study analyzes drug-induced delirium (DID) during treatment with antidepressants and antipsychotics.
Results: A total of 436 565 psychiatric inpatients were treated with antidepressants and/or antipsychotics during the observation period from 1993 to 2016 in the participating 110 hospitals. Overall, 254 cases (0.06% of all patients treated with antidepressants and/or antipsychotics) of DID were detected. Implicated either in combination or alone (multiple drugs were implicated in 70.1% of DID), clomipramine (0.24%), amitriptyline (0.21%), and clozapine (0.18%) showed the highest incidence rates of DID. When implicated alone (98 cases overall), clozapine (0.11%) followed by amitriptyline (0.05%) were most likely causally associated with the occurrence of DID. Drugs with strong antimuscarinic properties generally exhibited higher risk of DID.
Conclusions: With an incidence rate of <0.1%, the use of antidepressants and antipsychotics was rarely associated with DID within the Arzneimittelsicherheit in der Psychiatrie program. Tricyclic antidepressants and clozapine were the most commonly implicated psychotropic drugs. These data support the specific role of antimuscarinic properties in DID.

Keywords: Adverse drug reactions, antidepressants, antipsychotics, delirium, drug surveillance

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Significance Statement

Delirium is a serious clinical syndrome often linked to the adverse effects of drugs with delirogenic properties. The present observational study analyzed drug-induced delirium (DID) during treatment with antidepressant (ADDs) and antipsychotic drugs (APDs) using data from AMSP (Arzneimittelsicherheit in der Psychiatrie), a multicenter drug surveillance program. A total of 254 cases of DID (0.06%) in 436 565 patients treated with APDs and ADDs were identified between 1993 and 2016 within the AMSP program. The use of ADDs and APDs was rarely associated with DID, with an incidence rate of <0.1% within the AMSP program. However, drugs with strong antimuscarinic properties, especially clozapine and amitriptyline, showed considerably higher rates. Since the AMSP project closely reflects the natural characteristics of psychiatric inpatient treatment, these data may be useful for clinicians prescribing psychotropic drugs in patients at risk of DID.

Introduction

Delirium is a clinical syndrome characterized by an acute change in mental functioning, including attention, awareness, cognitive function, and perception. Symptoms tend to fluctuate in presence, duration, and severity (Wilson et al., 2020). A recent meta-analysis detected an overall prevalence of 23% among medical inpatient settings (Gibb et al., 2020), making it one of the most common diagnoses made by psychiatric consultation services (Grover et al., 2009) and particularly prevalent among elderly patients exposed to polypharmacy (Mulkey et al., 2018). Delirium develops when new noxious stimuli overstrain an organism that is already vulnerable by preexisting risk factors and is thought to involve alterations in several neurotransmitter systems (Morandi et al., 2015; Friedrich et al., 2018; Wilson et al., 2020). Drug-induced delirium (DID) is thought to be mediated by disturbances in neurotransmission. Cholinergic deficiency and dopamine excess are by far the most frequently explored mechanisms and likely also mediate the deliriogenic effects of many CNS drugs, which rank highest among the potentially reversible precipitating factors associated with delirium (Mulkey et al., 2018). Though less understood, other relevant pathways potentially involved in DID include histamine, γ-aminobutyric acid, serotonin (5-hydroxytryptamine), and noradrenaline (Maldonado, 2018; Mulkey et al., 2018; Wilson et al., 2020).

Common adverse effects of drugs with strong antimuscarinic properties include cognitive impairment (Bishara et al., 2017), falls, urinary retention, psychosis, and DID, with multiple studies showing a positive association between antimuscarinic drugs and DID (Campbell et al., 2009). Clozapine is one of the most potent centrally acting antimuscarinic drugs in common use (Bishara et al., 2017). Its potential to induce DID is still of particular interest and has been related to its marked antimuscarinic properties (Das et al., 2020). Similarly, adverse effects of tricyclic and tetracyclic antidepressants have been associated with their antimuscarinic (Bishara et al., 2017) as well as antihistaminergic and anti-alpha1-adrenergic properties (Frey et al., 2000; Gillman, 2007). Older adults are more prone to these effects because of age-related decreases in cholinergic neurons in the CNS but also due to indirect mechanisms such as impaired clearance and increased blood-brain barrier permeability of pharmacological agents (Low et al., 2009; Bishara et al., 2017; Mulkey et al., 2018; Pasina et al., 2019). Given the known potential of some antidepressants or antipsychotic drugs to precipitate DID, the present report estimates the risk for DID attributable to antidepressants or antipsychotics prescribed in a large sample of psychiatric inpatients.

METHODS

AMSP Program

The AMSP (German: "Arzneimittelsicherheit in der Psychiatrie", drug safety in psychiatry) program aims to continuously detect severe and unusual adverse drug reactions (ADRs) occurring during psychopharmacological treatment during inpatient care. ADRs assessed in the AMSP program are defined as adverse reactions to psychotropic drugs at appropriate doses for therapeutic or prophylactic treatment (adverse reactions occurring due to intoxication or inefficiency are not included in the AMSP database). Only severe ADRs, defined as (potentially) life-threatening or seriously endangering the patient's health, considerably impairing everyday functioning, or requiring the patient's transfer to another department or ward providing more intensive care are considered. For this analysis, data from 110 university, municipal- or state psychiatric hospitals in Germany, Austria, and Switzerland are included.

Collection, Assessment, and Calculation of Relative Frequency of ADRs

Information on severe ADRs is documented regularly by psychiatrists as drug monitors using a standardized questionnaire, including the patient's demographics, complete medication, and characteristics of the ADR such as relevant risk factors, previous exposure to the drug(s) in question, alternative hypotheses on the cause of the ADR, and measures undertaken. Senior doctors of each hospital review the cases that are later discussed at regional and central case conferences occurring twice per year. Participants comprise hospital drug monitors, representatives from the national drug regulatory authorities, and drug safety experts from the pharmaceutical industry. Following discussions and analyses, ADR probability ratings are assigned and sent to the relevant authorities. Case questionnaires are stored in the AMSP central database.

Probability ratings for ADRs are performed based on the proposals of Hurwitz and Wade as well as Seidl et al. (Seidl, 1966; Hurwitz and Wade, 1969) and the AMSP study guidelines (Grohmann et al., 2004). The ADR probability rating system defines the following grades of probability, beginning with Grade 1 in which the ADR is deemed possible, that is, the risk of the ADR is not known and the probability of an alternative cause other than the drug in question is estimated >50%. Grade 2 is defined as probable, with a known reaction, time course, and dosage for a specific drug. The likelihood of alternative causes is estimated at <50%. Grade 3 is defined as definite, meaning that in addition to the criteria for a probable rating, reexposure to the drug led a reemergence of the ADR. Grade 4 signifies cases with questionable information or insufficient documentation. For this analysis, only cases of DID with a probable or definite rating for at least 1 antipsychotic or antidepressant were included.

In many cases, however, more than 1 drug is implicated in causing DID. When a pharmacodynamic interaction is held responsible for an ADR, causality of each of the implicated drugs is rated "possible," "probable," or "definite." These 2 scenarios are

examined separately: ADRs in which a single antidepressant/antipsychotic was held accountable for DID (i.e., without implication of other drugs) are referred to as "implicated alone." Cases in which multiple drugs were held accountable for DID are included in the second group of ADRs ("implicated at all"), which includes all cases of DID occurring during treatment with 1 or more antidepressant or antipsychotic (Fig. 1).

For calculation of the relative frequencies of the occurrence of a specific ADR, data on drug use are assessed in all patients at all hospitals participating in the AMSP project on 2 reference days per year. On those reference days, all administered drugs and dosages are assessed along with demographic and diagnostic data from all inpatients currently in treatment. The contributing hospitals further provide the number of inpatients under surveillance per year to extrapolate the number of patients receiving each psychotropic drug as well as the median dosages in all treated patients from the sample data. These data allow for an estimation of drug use over the course of 1 year (Grohmann et al., 2004).

Statistical Methods

Statistical comparisons of DID rates related to diagnoses, gender, and age were performed by means of chi-square tests. Incidence rates of DID were calculated based on inpatients receiving antipsychotics and antidepressants and are presented together with their 95% exact confidence intervals (CIs) (Clopper and Pearson, 1934). Significance level was set at $P < .05$. The CIs of substances with no cases of delirium were approximated by 0.01 instead of 0. The CI was calculated according to the exact method and not one of the approximation methods (Vollset, 1993) due to the low actual ADR incidence rates and the high number of individual patients exposed. Due to power considerations, psychotropic drugs with an estimated number of <5000 exposed patients were excluded from statistical analysis.

Ethics Review

Evaluations based on the AMSP database have been approved by the Ethics Committee of the University of Munich and the Ethics Committee of the Hannover Medical School (no. 8100_BO_S_2018). This study adheres to the Declaration of Helsinki and its later amendments. The AMSP program is a continuous, observational, post-marketing drug surveillance program and does not interfere with the ongoing clinical treatment of patients under surveillance.

RESULTS

Demographic and Illness-Related Data

During the observation period from 1993 to 2016, 495 615 psychiatric inpatients at 110 hospitals were monitored by the AMSP program. As estimated from the sample data, 436 565 patients (88.1%) received antidepressants and/or antipsychotics. Among these patients, 254 cases of DID were detected (0.06%). DID accounted for 5.1% of all severe ADRs during antidepressant/antipsychotic treatment within this period, making it the third-most-common severe ADR, following weight gain (8.7%) and elevated liver enzymes (7.6%). Table 1 shows the demographic data of all patients treated with antidepressants/antipsychotics under surveillance compared with those with DID. Most patients with DID suffered from mood disorders (52.8% of patients with DID vs 37.9% of all patients treated with antidepressants/antipsychotics) and from schizophrenia (32.7% of patients with DID vs 35.6% of all patients treated with antidepressants/antipsychotics). Patients with mood disorders had a higher than average rate of DID (0.08%), whereas the rate of DID was lower in patients suffering from schizophrenia or organic disorders (0.05% each). While gender was equally distributed among patients with and without DID, significantly more patients with DID were older than 65 years.

Drugs Associated With Psychotropic DID

Table 2 shows the number of DID cases, incidence rates, and their respective 95% CIs for all implicated antipsychotics and antidepressants prescribed in >5000 patients during the observation period. Figures 2–4 provide a graphical representation of the incidence rates with their exact 95% CIs for the individual compounds implicated at all or alone. Given the cases in which drugs were implicated at all, the highest risk of DID was found for clomipramine (0.24%), amitriptyline (0.21%), clozapine (0.18%), perazine (0.16%), levomepromazine (0.13%), and promethazine (0.11%). Regarding drugs implicated alone for the occurrence of DID, clozapine was implicated most often by far (41 cases; 0.11% or 65.1% of all cases where 1 antipsychotic was implicated alone). Only 3 other antipsychotics used in >5000 patients were implicated alone for DID in some cases: olanzapine, promethazine, and perazine. Among antidepressants, amitriptyline showed the highest rate of DID when implicated alone (0.05%). Three other tricyclic antidepressant drugs (TCAs; doxepin, clomipramine, and trimipramine) and the selective serotonin-norepinephrine reuptake inhibitor (SSNRI) venlafaxine were also implicated alone for DID. Among the drugs used in <5000 patients and implicated for DID, the TCA nortriptyline, used in 2535 patients, was involved in DID most often (i.e., in 13 cases and implicated alone in 5 cases). All 5 of these patients were 74 years of age or older. The short-acting i.m. preparation zuclopenthixol-acetate was used very rarely (n = 612) but was involved in 10 cases of DID, but never alone. In contrast, oral zuclopenthixol was administered more than 10 times as often but was implicated in only 5 DID cases (0.07%).

As can be seen in Table 2 and Figures 2–4, incidence rates differ greatly within subclasses of antipsychotics and antidepressants, even within groups of structurally related groups such as TCAs, phenothiazines, or thioxanthenes, so the drug subclasses are not compared. However, it is of note that no cases

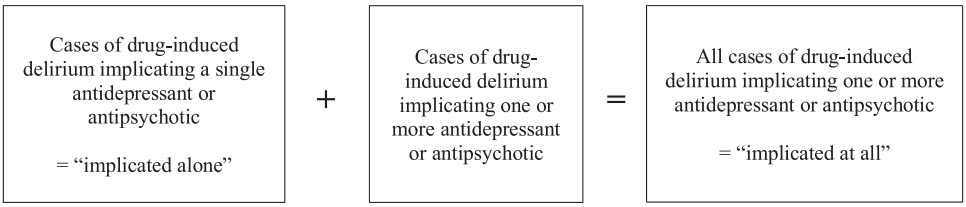

Figure 1. Definition of cases of drug-induced delirium: "implicated alone" vs "implicated at all.".

Table 1. Sociodemographic Data of Patients With Antipsychotic or Antidepressant-Induced Delirium Between 1993 and 2016

	All patients monitored, n	Percentage of all patients treated with psychotropic drugs	Patients with DID (n)	Percentage of DID cases	DID cases in % of all patients treated with psychotropic drugs	Chi-square test
Diagnosis (ICD-10)						
Organic Disorders (F0)	48 290	11.1	25	9.8	0.05	$\chi2=34.7$, df = 3, $P \leq .001$
Mood disorders (F3)	165 340	37.9	134	52.8	0.08	
Schizophrenia (F2)	155 518	35.6	83	32.7	0.05	
Others	67 417	15.5	12	4.7	0.02	
Total	436 565	100	254	100	0.06	
Age (y)						
≤64	343 688	78.7	161	63.4	0.05	$\chi2=35.7$, df = 1, $P \leq .001$
>64	92 877	21.3	93	36.6	0.15	
Total	436 565		254			
Sex						
Male	190 013	43.5	113	44.5	0.06	$\chi2=0.096$, df = 1, ns.
Female	246 552	56.5	141	55.5	0.06	
Total	436 565		254	100	0.06	

Abbreviations: Df, degrees of freedom; DID, drug-induced delirium; ICD-10, International Classification of Disease 10th Version; ns, not significant.

of DID were observed during treatment with butyrophenones, selective serotonin reuptake inhibitors, or noradrenergic and specific serotonergic antidepressants alone, whereas the SSNRI venlafaxine was implicated alone in 6 cases. In 4 of these cases, DID with single implication of venlafaxine occurred in patients ≥65 years of age (i.e., 0.05% of venlafaxine users ≥65 years), whereas only 2 cases affected patients <65 years (i.e., 0.006% of venlafaxine users <65 years). In contrast, duloxetine was implicated only once in combination and never alone.

DID With Implication of Multiple Psychotropic Drugs

Psychotropic drug combinations were held responsible in 178 of the 254 DID cases (70.1%). In 84 cases (33.1%), 2 drugs were implicated for the occurrence of DID, while combinations of 3 or more drugs were implicated in 94 cases (37.0%). Multiple implications were most often combinations of antipsychotics and antidepressants (64 cases, 25.1%); antipsychotics with antiparkinsonian drugs, mostly biperiden (38 cases, 15.0%); and 2 antipsychotics (35 cases, 13.8%). Combinations of antipsychotics with antiepileptic drugs were implicated in 29 cases (11.4%), antidepressants and antipsychotics with lithium as well as antidepressants with antiepileptic drugs in 26 cases each (10.24%). The most common triple implications were antidepressants with antipsychotics and lithium (n = 14), antidepressants with antipsychotics and antiepileptic drugs (n = 12), and 2 antipsychotics with antidepressants (n = 10).

Dose-Dependent Effects of DID

Table 3 shows the median drug dosages when the drug was implicated in patients experiencing DID either alone or at all as well as the estimated mean dosage in the reference sample. The median dosages of the psychotropic drugs administered were within the recommended range for each drug. There was a tendency for drugs associated with increased DID risk to be given in dosages that were similar or even lower in DID cases compared with the reference sample. In turn, drugs associated with decreased antipsychotic risk tended to be given in higher doses when implicated (Table 3). On the lower end of this distribution, clozapine was given in a median daily dosage of 200 mg in antipsychotic cases compared with a median dosage of 300 mg/d in the total sample. In contrast, the greatest differences between antipsychotic cases and the reference sample were found for promethazine, which was prescribed in a median daily dosage of 150 mg in antipsychotic cases, while the median daily dosage in the reference sample was just 50 mg and for perazine 200 mg in the reference sample and 600 mg implicated alone. In 3 of the 6 cases of DID with a single implication of venlafaxine, the patients received ≥225 mg/d. The mean dosage for amitriptyline when delirium occurred was 100 mg/d with a maximum of 350 mg when amitriptyline was prescribed.

Risk Factors, Countermeasures, and Course of Psychotropic DID

Risk factors are not available for the total population exposed to antipsychotics and/or antidepressants but were documented for the ADR cases. In 98 cases (38.6%), no known risk factors could be identified. A total of 61.4% of patients with DID had preexisting risk factors, predominantly organic brain damage in 95 cases (37.4% of all cases of DID). This was documented as primary diagnosis in only 21 cases (8.3%) and as comorbid diagnosis in the remaining 74 cases (29.1%). In 55% of cases in which a drug was implicated alone, the dosage of the implicated antipsychotic/antidepressant was increased very quickly, while treatment was imitated using a high starting dose in 21.1% of cases with implication of a single drug.

In 26% of DID cases, the dosage of 1 implicated drug was reduced, and in 89%, at least 1 of the implicated drugs was discontinued. Drugs to treat DID were prescribed in 44% of all cases. In the first year of the observation period, haloperidol was the most used antipsychotic to treat DID. In the following years, mostly risperidone was used. Physostigmine was rarely used. In 16% of cases, the patients required a transfer to another ward to receive more specialized care due to the occurrence of DID.

Table 2. Delirium Induced by Antipsychotic and Antidepressant Drugs Between 1993 and 2016

Antipsychotic drugs	Patients receiving drug	All cases of DID			Cases of DID implicate to a single drug		
Antidepressant drugs	n	n	95% CI	%	n	95% CI	%
All antipsychotics	333175	178	0.05	0.06-0.04	63	0.02	0.02-0.01
Butyrophenones							
Haloperidol	37650	0	0.04	0.04–0.04	0	—	—
Pipamperone	24117	1	0.04	0.04–0.05	0	—	—
Melperone	18984	2	0.03	0.03–0.03	0	—	—
Thioxanthenes							
Flupentixole	10823	0	0	0.03–3.2E	0	—	—
Flupentixoledecanoate	5825	1	0.02	0.10–0.00	0	—	—
Chlorprotixene	14017	6	0.04	0.09–0.01	0	—	—
Zuclo-/Clopentixole	8320	6	0.07	0.16–0.02	0	—	—
Phenothiazines							
Prothipendyl	15742	5	0.03	0.07–0.01	0	—	—
Perazine	15495	25	0.16	0.24–0.10	1	0.01	0.04-0.00
Levomepromazine	13374	17	0.13	0.20–0.07	0	—	—
Promethazine	17546	20	0.11	0.18–0.07	3	0.02	0.05-0.00
SGAs							
Clozapine	38349	69	0.18	0.23–0.14	41	0.11	0.15-0.07
Olanzapine	54822	25	0.05	0.07–0.03	4	0.01	0.02-0.00
Quetiapine	66209	20	0.03	0.05–0.01	0	—	—
Aripiprazole	15988	0	0	0.02–2.2E	0	—	—
Risperidone	51683	1	0.03	0.01–0.00	0	—	—
Amisulprid	14168	0	0	0.03–2.4E	0	—	—
All antidepressants	243588	140	0.06	0.07–0.04	35	0.01	0.02-0.01
TCAs							
Amitryptiline	14089	29	0.21	0.30–0.13	7	0.05	0.30-0.13
Doxepin	13811	7	0.05	0.10–0.02	1	0.01	0.10-0.02
Clomipramine	6174	15	0.24	0.40–0.13	1	0.02	0.40-0.13
Trimipramine	13604	5	0.04	0.09–0.01	1	0.01	0.09-0.01
SSRIs							
Fluoxetine	5849	1	0.02	0.10–0.00	0	—	—
Paroxetine	10298	9	0.09	0.17–0.04	0	—	—
Citalopram	24904	8	0.03	0.06–0.01	0	—	—
Sertraline	21868	5	0.02	0.05–0.00	0	—	—
Escitalopram	25667	6	0.02	0.05–0.00	0	—	—
SSNRIs							
Venlafaxine	41599	18	0.04	0.07–0.02	6	0.01	0.07-0.02
Duloxetine	14343	1	0.01	0.04–0.00	0	—	—
Other antidepressants							
Mirtazapine	60305	19	0.03	0.05–0.01	0	—	—
Trazodone	12571	5	0.04	0.09–0.01	0	—	—

Abbreviations: CI, confidence interval; DID, drug-induced delirium; SGA, second-generation antipsychotic drug; SSNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant drug.
Incidence rates for the individual drugs are given in percentages and presented together with their 95% confidence intervals (CIs). Only drugs used in >5000 patients are included.

Non-medical interventions were necessary in 15% of cases, and 9% of patients with DID were attended to by a liaison doctor from other medical specialties. DID remitted in 98.4% of cases while in 4 cases (1.6%) it was still in remission at the end of the observation period. No case of DID was immediately life-threatening.

DISCUSSION

The risk for delirium likely arises as an interaction between predisposing vulnerability factors, such as advanced age and preexisting cognitive impairment, and precipitating factors, such as sleep deprivation, malnutrition, a history of substance abuse, polypharmacy, and use of certain drugs such as opioids or CNS depressants (Wilson et al., 2020). The present results are in line with this pathophysiological model as drug induced delirium was significantly higher in the elderly and most patients exhibited preexisting risk factors such as organic brain damage (though, due to study design, no comparison with the reference sample can be given). Apart from intrinsic risk factors, rapid dose escalation or an unusually high starting dose may precipitate DID. Both of these circumstances are well-known for increasing the risk of ADRs, and they were observed in most cases where a drug was implicated alone (overall 76.1%)

Interestingly, incidence of DID was highest among patients with a mood disorder, potentially related to the more frequent use of TCAs, some of which exhibited the highest risk of DID in our sample. Compared the prevalence of organic brain disorder as the primary diagnosis in the general

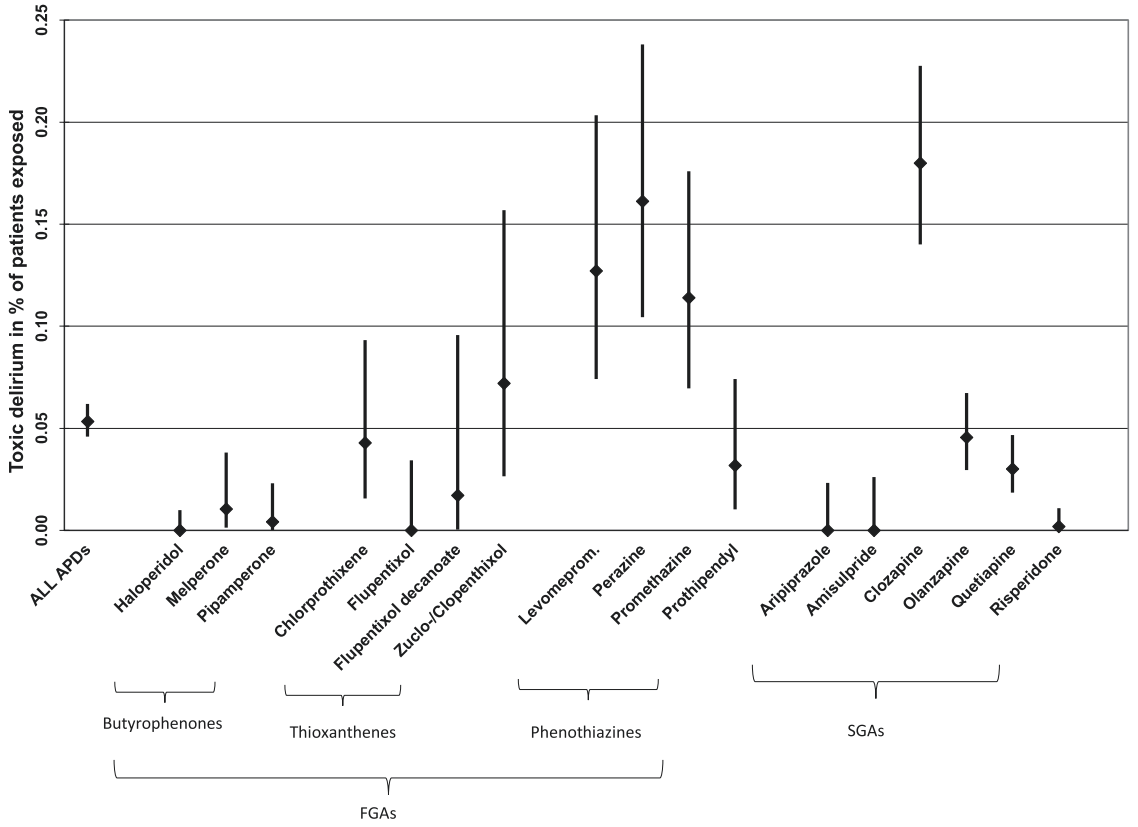

Figure 2. Incidence rates of drug-induced delirium for antipsychotic drugs in percentage with 95% confidence intervals (CIs) when drugs were implicated at all; only drugs prescribed more than 5000 times are depicted.

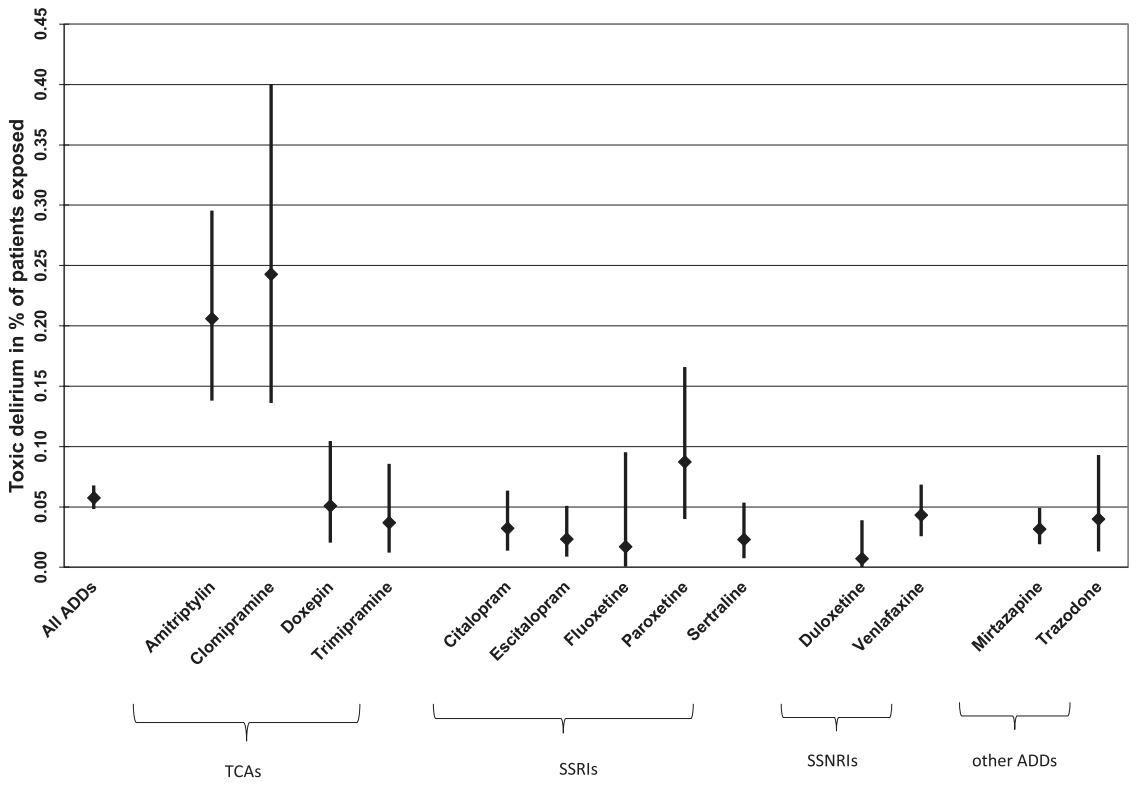

Figure 3. Incidence rates of drug-induced delirium for antidepressant drugs in percentage with 95% confidence intervals (CIs) when drugs were implicated at all; only drugs prescribed more than 5000 times are depicted.

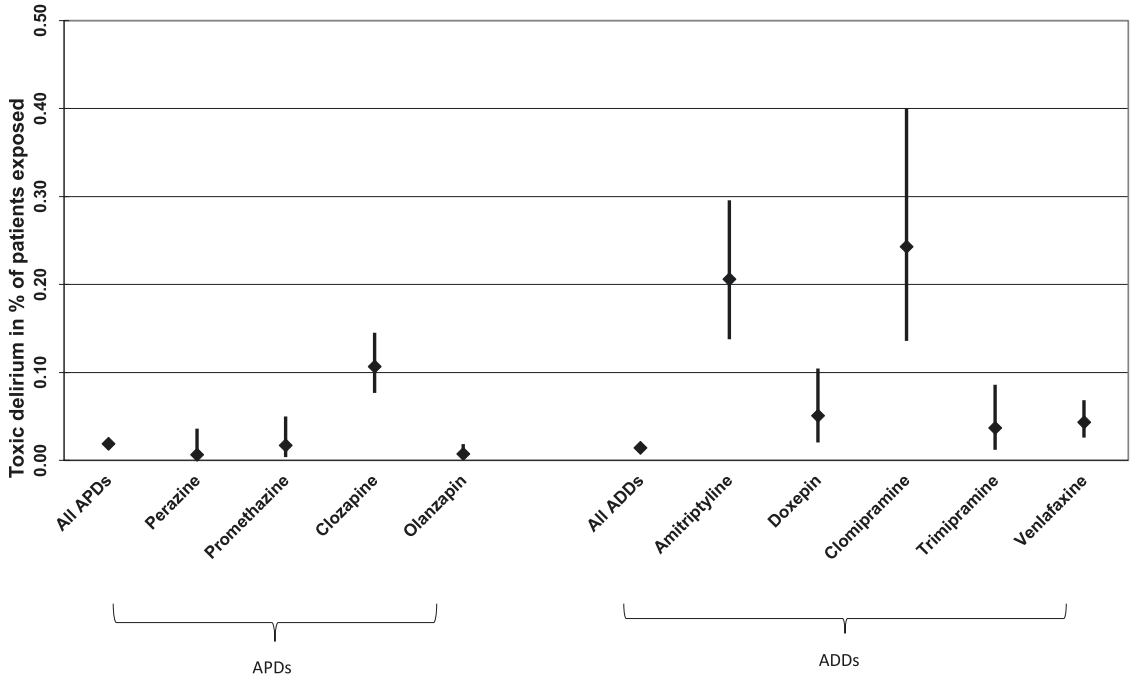

Figure 4. Incidence rates of drug-induced delirium for antipsychotic drugs and antidepressant drugs in percentage with 95% confidence intervals (CIs) when drugs were implicated alone; only drugs prescribed more than 5000 times and implicated at least in 1 case are depicted.

Table 3. Median Dosages (in mg) of Psychotropic Drugs in Patients (1993–2016)

		Patients with drug-induced delirium (median dosage in mg)	
Psychotropic drugs	All treated patients (median dosage in mg)	All cases (dosages in mg)	Drug implicated alone (dosages in mg)
Amitriptyline	100	100	100
Chlorprothixene	90	145	—
Citalopram	20	20	—
Clomipramine	125	125	100
Clozapine	300	200	200
Doxepin	100	125	125
Escitalopram	10	15	—
Levomepromazine	100	100	—
Mirtazapine	30	30	—
Olanzapine	15	10	10
Paroxetine	30	40	—
Perazine	200	200	600
Promethazine	50	150	150
Prothipendyl	80	80	—
Quetiapine	200	400	—
Sertraline	100	150	—
Trazodone	150	150	—
Trimipramine	100	50	50
Venlafaxine	150	150	187.5
Zuclopenthixol	30	25	—

Among all treated patients per drug, among patients with DID occurrences per drug, and among patients with DID occurrences per drug implicated alone.

study population, relatively fewer patients with such a primary diagnosis developed DID. This finding indicates that clinicians may have exercised more caution when prescribing drugs with a stronger delirogenic potential to these particularly vulnerable patients. However, this pertains only to patients with a primary psychiatric diagnosis of an organic disorder; 29% of patients with other primary diagnoses suffered from some form of co-morbid, preexisting organic brain damage as a risk factor for DID, demonstrating that the treating physicians may have taken less into consideration a nonprimary diagnosis of organic brain damage when establishing pharmacotherapy.

In a systematic review, Clegg and Young (2011) evaluated the association between drug class and risk of DID and found the highest risk of DID among patients treated with opioids, benzodiazepines, dihydropyridine calcium channel antagonists, and histamine H1-receptor antagonists (e.g., diphenhydramine, dimetindene). The risk of DID of histamine H2-receptor antagonists (e.g., cimetidine, ranitidine), TCAs, antiparkinsonian drugs, corticosteroids, nonsteroidal antiinflammatory drugs, and antimuscarinic drugs was less certain (Clegg and Young, 2011).

While Clegg and Young reported no increased risk of DID under treatment with antipsychotics (Clegg and Young, 2011), our results suggest that risk of DID shows relevant differences among individual antipsychotics: clozapine exhibited the strongest association when drugs were implicated alone, but the phenothiazines perazine, levomepromazine, and promethazine were also significantly associated with DID. In contrast, several antipsychotics showed significantly lower risk, namely amisulpride, aripiprazole, flupentixol, risperidone, and haloperidol, with the latter being implicated not even once despite use in 37 650 inpatients. Given that many of these drugs are recommended in the treatment of DID, it seems possible that some of these drugs have preventive effects on delirium risk, though our study design is not capable of ascertaining this assumption.

Antimuscarinic Properties of Psychotropic DID

Certain drugs are well-known as precipitating factors of delirium, especially antipsychotics and antidepressants with strong anticholinergic—or more precisely, antimuscarinic—properties. Antimuscarinic delirium is associated with antagonism of postsynaptic type 1 antimuscarinic receptors (Dawson and Buckley, 2016). Antimuscarinic DID is a potential complication of drugs with central antimuscarinic activity and is most often observed in the elderly (Mulkey et al., 2018).

Especially when examining implications of single drugs, we found drugs with the strongest antimuscarinic properties (i.e., promethazine, clozapine, amitriptyline) (Gerretsen and Pollock, 2011; Siafis et al., 2018; Cookson, 2019) were most often causally associated with delirium. Clozapine, the antipsychotic with the highest antimuscarinic potential (de Leon, 2005), was the psychotropic drug most often implicated alone (i.e., in 41 cases). Similarly, amitriptyline shows the highest affinity to muscarinic acetylcholine receptors (Gillman, 2007) among antidepressants and was the antidepressant with the second highest risk of single-implication DID following clomipramine. The comparably low number of DID cases with single implication of promethazine may be in part explained by the fact that promethazine is often used as an additional sedative agent in combination with other psychotropic drugs. In cases in which a single drug with only moderately strong affinity to antimuscarinic acetylcholine receptors was implicated [i.e., olanzapine, doxepin, clomipramine, and trimipramine (Gillman, 2007; Leucht et al., 2014; Siafis et al., 2018)], the affected patients may have had more intrinsic risk factors such as organic brain damage. Despite their antimuscarinic properties, quetiapine was never and olanzapine only rarely implicated alone as causative of DID.

The combined effect of drugs with only moderately strong antimuscarinic activity may add up to cumulative antimuscarinic effects strong enough to precipitate DID. For example, perazine, a phenothiazine with moderate affinity to the muscarinic acetylcholine receptor (Leucht et al., 2014), was causally associated with the occurrence of DID in combination with other drugs in 25 cases, whereas only a single case of DID was documented in which perazine was implicated alone. Moderately strong antimuscarinic effects may also explain the risk of DID associated with quetiapine (Siafis et al., 2018) and the low-potency first generation antipsychotics levomepromazine (Obara et al., 2019) and chlorprothixene (Ozbilen and Adams, 2009). Also, though never implicated alone, paroxetine was the SSRI most likely causally associated with the occurrence of DID (9 cases), probably because it is the SSRI with the most pronounced antimuscarinic properties (Gray and Hanlon, 2016). Several of the above-mentioned drugs (e.g., low-potency first generation antipsychotics) are more likely to be used in combination with other psychotropic drugs, which may explain their higher risk of DID in cases with multiple implications. As 2 or more drugs were held responsible in the majority (70.1%) of cases, our data support the concept of cumulative antimuscarinic effects. Accordingly, our results are in line with central antimuscarinic activity being an essential pathomechanism of delirium.

DID Associated With Antagonism of Histamine Receptors

DID is a well-known side effect of first-generation H1 antihistamines (e.g., diphenhydramine, dimenhydrinate, doxylamine), but it is also associated with antagonism of H2 receptors. Histamine is involved in the regulation of mood, cognition, attention, and arousal and likely plays a critical role in the pathophysiology of DID. Accordingly, concerns have been raised when prescribing antihistamine H1 or H2 receptor antagonists to people at risk for delirium (Chazot et al., 2019). Several of the implicated drugs in our sample have prominent antihistaminergic effects. Interestingly, all psychotropic drugs with strong H1 receptor antagonism (e.g., promethazine, clozapine, olanzapine, doxepin, amitriptyline, nortriptyline) significantly associated with DID in our data are also characterized by strong to moderate antimuscarinic effects (Gillman, 2007; Siafis et al., 2018; Chazot et al., 2019). Therefore, our results do not necessarily support a general delirogenic effect of central H1 antagonism but rather an interaction of some antihistamines with muscarinic receptors (Brown, 2000). This theory is further supported, for example, by pipamperone, which exhibited a low risk for DID in our sample and has recently shown potential in treatment of delirium (Boettger et al., 2017). Pipamperone is a low-potency antipsychotic with marked sedative effects but negligible antihistaminergic and antimuscarinic properties (Li et al., 2016). Quetiapine, a drug with potent antagonistic activity at the histamine H1 receptor and only moderate antimuscarinic properties (Siafis et al., 2018), was also associated a lower-than-average risk of DID in our sample.

DID Mediated by Other Pathways of Neurotransmission

Apart from TCAs, venlafaxine was the only antidepressant to be implicated alone in DID. As venlafaxine is an SSNRI displaying neither strong antimuscarinic nor antihistaminergic properties, other mechanisms must mediate its delirogenic potential. Venlafaxine blocks the reuptake of serotonin, noradrenaline, and—when applied at a high dose—dopamine (Raouf et al., 2017) and therefore influences 3 different pathways of neurotransmission that have been associated with DID (Cascella et al., 2018; Wilson et al., 2020). The reuptake of dopamine occurs primarily when administered at doses of 225–300 mg/d (Raouf et al., 2017), which was used in 3 out the 6 patients with

venlafaxine-induced delirium. An excess of dopamine is associated with dysregulation of the sleep-wake cycle, arousal, and psychosis (Mulkey et al., 2018). Serotonergic neurons are involved in functions such as aggressive and impulsive behavior, circadian rhythm, cognition, attention, and sexuality (Pourhamzeh et al., 2021), whereas noradrenergic neurons modulate attention, motivation, and attention (Ranjbar-Slamloo and Fazlali, 2020), all of which may be disturbed in patients with delirium (Maldonado, 2018). With a 12-fold higher risk of venlafaxine-induced delirium, older patients (i.e., ≥65 years of age) appear more susceptible to these effects than those aged <65 years. Other authors have postulated a link between venlafaxine's potential to induce DID in the context of serotonin syndrome and hyponatremia (Pfeffer and Grube, 2001; Howe and Ravasia, 2003; Grover et al., 2013), however, cases of DID occurring independently from these circumstances have previously been described, suggesting that venlafaxine's effects on the reuptake of serotonin and noradrenaline alone may suffice in causing DID (Alexander and Nillsen, 2011; del Río-Casanova et al., 2015).

Study Limitations

The data obtained in this naturalistic study have several limitations. Drug use data have not been available for the total sample but have been estimated from systematic data collection at 2 d/y. Observation bias cannot entirely be excluded as the reporting in AMSP is provided by clinicians acting as individual drug monitors and therefore is up to the drug monitors' clinical experience and motivation. Therefore, cases could remain undetected and result in lower incidence rates, especially in the case of hypomotoric delirium, which is often underrecognized. In addition, we can neither ascertain compliance with drug intake nor give statements on the involvement of pharmacokinetic effects, as therapeutic drug monitoring is not routinely available in many of the included departments. Regarding generalizability, it is important to note that in this analysis, delirium was defined by the psychiatric ICD-10 criteria, while standardized instruments and diagnostic algorithms such as the Confusion Assessment Method are generally preferred in research (Inouye et al., 1990). Our data, therefore, also do not differentiate between hypermotoric and hypomotoric delirium. Hypomotoric delirium generally predominates in medical or surgical wards as well as in intensive care units (Girard et al., 2018). Also, though overlapping pathogenic mechanisms are likely relevant to all cases of delirium, our results only apply to psychiatric inpatients, and many of the psychotropic drugs reported here are only rarely prescribed outside of psychiatric wards. However, as postoperative delirium is the most prevalent and most frequently studied subtype of delirium (Cascella et al., 2018), our data may be specifically valuable concerning the understudied group of psychiatric inpatients with DID.

CONCLUSION

A total of 254 cases of DID (0.06%) in 436 565 patients treated with antipsychotics and antidepressants were identified between 1993 and 2016 within the AMSP program. Overall, antidepressants and antipsychotics in general appear to have a low risk of DID. Risk of DID varies significantly among individual antidepressants and antipsychotics, which appears to correlate in particular with the presence of strong antimuscarinic properties, especially clozapine and amitriptyline. Drugs with moderately high affinity to postsynaptic type 1 antimuscarinic receptors such as the phenothiazines perazine and levomepromazine are more likely to cause DID when combined with other delirium-inducing drugs. Antihistaminergic as well as serotonergic and noradrenergic properties also appear to contribute to the risk of DID, of which the latter 2 seem to contribute to venlafaxine's risk of DID. Venlafaxine was the only drug implicated as single cause of DID that does not have relevant antimuscarinic and/or antihistaminergic properties. More than 1 drug was considered responsible in most cases of DID (70.1%), consistent with an important role of polypharmacy in DID. About 60% of patients with antipsychotic-/antidepressant-induced delirium had predisposing risk factors for delirium, most commonly organic brain damage. When drugs were implicated alone, rapid dose escalation or high starting dose presented as a risk factor in three-quarters of these cases. Patients ≥65 years of age had a threefold higher risk of developing DID than those aged <65 years. Since the AMSP project closely reflects the natural characteristics of psychiatric inpatient treatment, the present results may provide useful supplementary information for clinicians in view of the risk of DID with noncombined or combined psychotropic drug therapies. Further research is needed to provide a deeper understanding of the pathophysiological mechanisms and changes in neural transmission underlying delirium. The latter would help us in selecting an appropriate and efficacious psychopharmacological treatment regimen specifically focusing on the affected transmitter systems and perhaps aid in preventing delirium in patients at high risk for delirium.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Interest Statement

R.G. and S.T. are involved in the project management of AMSP. S.T. has been a member of an advisory board for Otsuka and Janssen Cilag and has received speaker`s honoraria from Janssen Cilag, Lundbeck, Otsuka, Recodati Pharma GmbH, and Servier. J.S. took part in an educational event sponsored by Otsuka/Lundbeck. S.K. has received grants/research support, consulting fees, and/or honoraria within the last 3 years; grant/research support from Lundbeck; he has served as a consultant or on advisory boards for Celegne, IQVIA, Janssen, Lundbeck, Mundipharma, Recordati, Takeda, and Schwabe; and he has served on speaker's bureaus for Angelini, Aspen Farmaceutica S.A., Janssen, Krka Pharma, Lundbeck, Medichem Pharmaceuticals Inc., Neuraxpharma, OM Pharma, Pierre Fabre, Sanofi, Servier, Schwabe, and Sun Pharma. D.W. received lecture fees/authorship honoraria within the last 3 years from Angelini, Lundbeck, MedMedia Verlag, and Medical Dialogue. R.F. received speaker`s honoraria from Janssen-Cilag and Lundbeck. All other authors state they have no conflicts of interest to declare.

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GmbH, Duphar Pharma GmbH & Co. KG, Eisai GmbH, esparma GmbH Arzneimittel, GlaxoSmithKline Pharma GmbH & Co. KG, Hoffmann-La Roche AG Medical Affairs, Janssen-Cilag GmbH, Janssen Research Foundation, Knoll Deutschland GmbH, Lilly Deutschland GmbH Niederlassung Bad Homburg, Lundbeck GmbH & Co. KG, Novartis Pharma GmbH, Nordmark Arzneimittel GmbH, Organon GmbH, Otsuka-Pharma Frankfurt, Pfizer GmbH, Pharmacia & Upjohn GmbH, Promonta Lundbeck Arzneimittel, Rhone Poulenc Rohrer, Sanofi-Synthelabo GmbH, Sanofi-Aventis Deutschland, Schering AG, SmithKlineBeecham Pharma GmbH, Solvay Arzneimittel GmbH, Synthelabo Arzneimittel GmbH, Dr Wilmar Schwabe GmbH & Co., Thiemann Arzneimittel GmbH, Troponwerke GmbH & Co. KG, Upjohn GmbH, Wander Pharma GmbH, and Wyeth-Pharma GmbH; and (3) Swiss companies: AHP (Schweiz) AG, AstraZeneca AG, Bristol–Myers Squibb AG, Desitin Pharma GmbH, Eli Lilly (Suisse) S.A., Essex Chemie AG, GlaxoSmithKline AG, Janssen-Cilag AG, Lundbeck (Suisse) AG, Mepha Schweiz AG/Teva, MSD Merck Sharp & Dohme AG, Organon AG, Pfizer AG, Pharmacia, Sandoz Pharmaceuticals AG, Sanofi-Aventis (Suisse) S.A., Sanofi Synthelabo SA, Servier SA, SmithKlineBeecham AG, Solvay Pharma AG, Vifor SA, Wyeth AHP (Suisse) AG, and Wyeth Pharmaceuticals AG. Dr Konstantinidis is involved in the project management of the Austrian division of AMSP.

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