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# Cardiovascular Adverse Reactions During Antipsychotic Treatment: Results of AMSP, A Drug Surveillance Program Between 1993 and 2013

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## Abstract

**Background:** Cardiovascular diseases are still the leading cause of global mortality. Some antipsychotic agents can show severe cardiovascular side effects and are also associated with metabolic syndrome.
**Methods:** This observational study was based on data of AMSP (Arzneimittelsicherheit in der Psychiatrie), a multicenter drug surveillance program in Austria, Germany and Switzerland, that recorded severe drug reactions in psychiatric inpatients.
**Results:** A total of 404 009 inpatients were monitored between 1993 and 2013, whereas 291 510 were treated with antipsychotics either in combination or alone. There were 376 cases of severe cardiovascular adverse reactions reported in the given timespan, yielding a relative frequency of 0.13%. The study revealed that incidence rates of cardiovascular adverse reactions were highest during treatment with ziprasidone (0.35%), prothipendyl (0.32%), and clozapine (0.23%). The lowest rate of cardiovascular symptoms occurred during treatment with promethazine (0.03%) as well as with aripiprazole (0.06%). The most common clinical symptoms were orthostatic collapse and severe hypotonia, sinustachycardia, QTc prolongation, myocarditis, and different forms of arrhythmia. The dosage at the timepoint when severe cardiovascular events occurred was not higher in any of the given antipsychotics than in everyday clinical practice and was in average therapeutic ranges. In terms of subclasses of antipsychotics, no significant statistical difference was seen in the overall frequencies of adverse reactions cases, when first-generation high potency, first-generation low potency, and second-generation antipsychotics were compared. Thirty percent of adverse events among second-generation antipsychotics were induced by clozapine.
**Conclusions:** Our findings on cardiovascular adverse reactions contribute to a better understanding of cardiovascular risk profiles of antipsychotic agents in inpatients.

**Keywords:** adverse drug reaction, antipsychotics, drug surveillance, cardiovascular

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### Significance Statement

Psychotropic drugs can cause severe adverse events affecting the cardiovascular system. This research article explores severe events caused by antipsychotic agents. Lately, special focus in research was given to QTc prolongations, but hypo- and hypertension as well as myocarditis, arrhythmias, myocardial infarction, and heart failure are also reported as possible severe adverse events in association with antipsychotic treatment. Gathering more in-depth knowledge about the latter might provide more awareness, especially when preexisting risk factors are recognized.

## Introduction

Despite progress in prevention and treatment, cardiovascular disease remains the leading cause of mortality globally and the most common cause of natural mortality in schizophrenia. Adverse effects linked to antipsychotics are likely to contribute to cardiometabolic and endocrine adverse events constituting metabolic syndrome such as weight gain, dyslipidemia, and diabetes mellitus (Riordan et al., 2011). It is well known that first- as well as second-generation antipsychotics are linked to metabolic side effects and contribute to an increased risk of cardiovascular diseases (Pereira et al., 2018), although second-generation antipsychotics have been suggested to induce greater weight gain and cause more metabolic problems than first-generation antipsychotics (Szmulewicz et al., 2017). Antipsychotic medications with high or intermediate risk of metabolic abnormalities are associated with an almost 3-fold higher risk of major cardiovascular events. Szmulewicz et al. (2017) suggest to use "low-risk agents" such as aripiprazole, trifluoperazine, or ziprasidone since these agents were associated with lower incidence of major cardiovascular diseases during their retrospective cohort study. The exact mechanisms underlying the latter are not fully understood so far but may be linked to antagonistic activity at 5-$HT_{2A}$, 5-$HT_{2C}$, $M_3$ muscarinic receptors, or $H_1$ and alpha receptors (Roerig et al., 2011). Several atypical antipsychotic agents seem to have more potential for metabolic side effects than others, and despite a better understanding of the biochemical pathways and receptor-binding properties, the mechanisms remain unclear. Concerning cardiovascular function, there is also substantial evidence pointing to a relationship between antipsychotic (AP) treatment and prolongation of QT interval (Brunton et al., 2011; Leucht et al, 2013). Antipsychotic-induced prolongation of corrected QT interval (QTc) is a major concern as this may increase risk of Torsades de Pointes arrhythmia and eventually lead to sudden death (Glassman et al., 2001). The frequency of QTc-related arrhythmias in AP-treated psychiatric patients has been estimated at 8%, leading to a rate of sudden unexpected death twice that observed in normal populations (Welch et al., 2000). Although the molecular mechanisms linking AP to QT prolongation have not been fully elucidated yet, there is evidence pointing to a direct effect on certain subtypes of myocardial ion channels, particularly the human Ether-à-go-go-Related Gene (HERG) that encodes for a protein associated with a cardiac K+ channel involved in regulating repolarizing currents (Suessbrich et al., 1997; Rampe et al., 1998; Peireira et al., 2018). Myocarditis occurs in about 3% of those treated with clozapine, and cardiomyopathy may occur after myocarditis as well as from prolonged tachycardia. Well-known risk factors for clozapine-induced myocarditis are increasing age and rate of dose titration as well as concomitant sodium valproate administration (Ronaldson et al., 2012, 2017). Other serious cardiovascular adverse effects of antipsychotics include Brugada syndrome phenotype and myocardial infarction (Polcwiartek et al., 2016). There is evidence that any combination of 2 or more antipsychotic drugs increased the severity of adverse effects and hence for cardiovascular diseases (Wimmer et al., 2016; Szmulewicz et al., 2017).

## Methods

The AMSP program aims for a continuous detection of severe adverse drug reactions (ADRs) resulting from psychopharmacological treatment at adequate dosages for therapeutic or prophylactic treatment (ADRs 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 included in this AMSP analysis.

These ADRs are evaluated during inpatient treatment. For this analysis, data from 80 university, municipal, or state psychiatric hospitals in Germany, Austria, and Switzerland were included. Information on severe drug reactions is collected from colleagues on a regular basis by psychiatrists or drug monitors who use a standardized questionnaire to document cases. Information is collected on the details of adverse events as well as on patient demographics and complete medication. It includes alternative hypotheses on the causes of the ADR, relevant risk factors, measures undertaken, and previous exposure to the drug(s) in question. Senior doctors of each hospital review the cases that are later discussed at central and regional case conferences taking place twice a year. Participants comprise hospital drug monitors, representatives from the national authorities regulating drugs, and drug safety experts from the pharmaceutical industry. Following discussions and analyses, ADR probability ratings are assigned and sent to the relevant authorities, and pharmaceutical companies receive the case questionnaires that are also stored in the AMSP central database.

Probability ratings for ADRs were performed on the basis of the proposals of Hurwitz and Wade (1969) as well as Seidl et al. (1965) and AMSP study guidelines (Grohmann et al., 2004). The ADR probability rating system defines the following grades of probability beginning with Grade 1 in which ADR is possible, that is, the risk of ADR is not known and the probability of another 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 <50%. Grade 3 is categorized as definite, meaning a reexposure to the drug again causes the ADR. Grade 4 signifies questionable information or insufficient documentation.

In cases of polypharmacy more than 1 drug is often imputed. When a pharmacodynamic interaction is held responsible for an ADR, each of the imputed drugs is given a rating of "possible," "probable," or "definite" according to the given facts. In addition, data evaluation takes into account that each drug is imputed in

combination with others. Consequently, the AMSP data on ADR rates for a single drug or substance group distinguish between "all cases," including cases in which the drug or substance group in question was imputed in combination with others as well as those in which it was imputed alone.

For calculation of relative frequencies, data on drug use is assessed in all patients at the participating hospitals and are evaluated on 2 reference days per year. On those reference days, all administered drugs are assessed along with basic demographic and diagnostic data as well as detailed drug treatment records from all inpatients. Moreover, the contributing hospitals provide the number of inpatients and the mean treatment duration for all patients under surveillance per year.

### Cardiovascular ADRs

Severe cardiosvascular adverse reactions (CV ADRs) were defined according to the AMSP study guidelines as follows: cardiac failure; collapse; severe hypotension (symptomatic and systolic blood pressure <90 mmHg); severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >120 mmHg); arrhythmia, including bradycardia (heart rate <40 bpm); tachycardia (heart rate >120 bpm), atrial flutter, AV-block II° or III°, prolongation of heart rate-corrected QT interval (QTc); QTc >500 milliseconds or an increase of >60 milliseconds), or ventricular arrhythmia of at least Lown III or myocarditis. Fatal cases were included when a cardiac ADR as cause was documented. AMSP also assesses all cases of sudden unexplained deaths during AP treatment as an increase in mortality due to APs is known. However, these cases are not included here.

### Ethical Section

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 (Nr. 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.

### Statistical Analysis

Incidence rates of cardiovascular events were calculated as the percentage of inpatients receiving a special AP agent or subclass and presented together with their 95% confidence intervals (CIs). Regarding the low actual number of cases and the significant number of inpatients involved, the CI was calculated employing the exact method rather than one of the approximate methods (Vollset, 1993). The statistical program R was used to generate the figures (R Core Team, 2014). $\chi^2$ tests were calculated using IBM SPSS version 22.0. Significance was set at $P < .05$.

## Results

### Social Demographic and Illness-Related Data

During the observation period from 1993 to 2013, 404 009 psychiatric inpatients were monitored in the AMSP program at 80 hospitals. Among the reported classes of severe ADRs (e.g., neurological, psychiatric, urological, cutaneous, hematological, and hepatic ADRs, toxic delirium, hormone/electrolyte disturbances, and impaired sexual function) CV ADRs constituted almost 6% of all ADRs. In a total of 291 510 patients treated with APs, 376 cases of severe CV ADRs were recorded (all cases, 0.13%) and 72.2% of all patients (291 510 patients with AP medication out of 404 009 under surveillance) were treated with an AP agent. The diagnostic and sociodemographic data of all patients under surveillance and those with CV ADRs are given in Table 1. As to diagnosis, most CV ADR patients suffered from schizophrenia (52.4% vs 47.8% in all patients) and from organic disorders (14.6% vs 12.7%). The differences in diagnostic distribution were statistically significant. Also significantly more CV ADR patients were older than 65 years, whereas there was no difference in sex distribution.

Numbers and relative frequencies of all cases of severe CV ADRs during AP treatment with AP subclasses and single drugs are given in Table 2. Figure 1a-1b show the information for all individual agents given to more than 3000 patients imputed at all (Figure 1a) and imputed alone (Figure 1b). Data for APs such as sertindol, benperidol, bromperidol, paliperidone, sulpiride,

**Table 1.** Diagnostic and Sociodemographic Data

| | All patients monitored, n | % of Cases | Patients with cardiovascular ADRs, n | % of Cases | $\chi^2$ and P value |
|---|---|---|---|---|---|
| Diagnosis (ICD-10) | | | | | |
| Organic Disorders (F0) | 36 949 | 12.7 | 55 | 14.6 | $\chi2 = 14,3$, df = 3, $P < .003$ |
| Mood disorders (F3) | 80 505 | 27.6 | 102 | 27.1 | |
| Schizophrenia (F2) | 139 418 | 47.8 | 197 | 52.4 | |
| Others (F3) | 34 638 | 11.9 | 22 | 5.9 | |
| Total | 291 510 | | 376 | | |
| Age (y) | | | | | |
| <65 | 229 595 | 78.8 | 262 | 69.7 | $\chi2 = 18,6$, df = 1, |
| >65 | 61 915 | 21.2 | 114 | 30.3 | $P = .000017$ |
| Total | 291 510 | | 376 | | |
| Sex | | | | | |
| Male | 131 009 | 44.9 | 169 | 45.0 | $\chi2 = 0,00$, df = 1, P = n.s. |
| Female | 160 501 | 55.1 | 207 | 55.0 | |
| Total | 291 510 | | 376 | | |

zuclopentixol-acetat, fluspirilen, perphenazine, pimozide, thiazide, zotepine, and dixyrazine are not shown for the single drugs as they were prescribed <3000 times. Given the cases where drugs were imputed at all, ziprasidone, prothipendyl, and clozapine showed the highest rates with 0.35%, 0.32%, and 0.23%, respectively. However, for ziprasidone, CI intervals are wide due to its use in only just slightly more than 3000 patients (n=3176). As a single compound, clozapine was imputed in a total of 44 cases of 34 868 prescriptions (incidence rate 0.14%) showing the highest rate of drugs imputed alone. Clozapine was followed by ziprasidone (0.1%).

## Substance Classes of Antipsychotics and Severe CV ARDs

Subgroup analysis divided the prescribed AP agents in 3 subclasses: second-generation APs, first-generation low potency APs, and first-generation high potency APs. The events per substance class in percentage of exposed patients did not differ statistically significant between the subclasses (0.15%, 0.13%, and 0.13%, respectively). Second-generation agents were prescribed about 2 times more often than the other subclasses and showed 0.15% of events per substance class compared with 0.13% in first-generation low- and high-potency APs.

Types of severe CV ADRs are given in Table 3, showing hypotension and arrhythmias as the most frequently reported ADRs.

## Combination Treatment and Severe CV ADRs

Drug combinations were held responsible for severe CV ADRs in 264 cases (70.2%); the most frequent combination was that of an AP with another AP drug as well as the combination of an AP with an antidepressant (n=120 or 31.9% of all cases each) followed by the combination of an AP with a nonpsychopharmacological drug (n=71 or 18.9%) or a tranquilizer (n=50 or 13.3% of all cases). In 34 cases, (9.0%) APs were imputed in combination with 2 other drugs. Further information is given in Table 4 (supplemental material).

## Hypotension, Collapse, and Hypertension

Between 1993 and 2013, a total of 174 cases of hypotensive ADRs (0.03%, see Table 3) during AP treatment were recorded in the AMSP program. These cases accounted for almost one-half (41%) of the CV ADRs in this analysis.

Combinations were imputed in the majority of all hypotensive ADR cases (in 78.4%), most frequently those of APs with ADs (39.3% of all cases), antihypertensive drugs (31.8%), other APs (30.1%), and tranquilizers (27.2%). There were also 10 cases of combinations of an AP with hypnotics (n=10 or 7.35% of all hypotonia cases).

Imputed at all, prothipendyl (30 cases, 0.14%), pipamperone (32 cases, 0.1%), and chlorprothixene (18 cases, 0.09%) showed the highest incidence rates (Figure 2). For drugs imputed

**Table 2.** Cardiovascular Adverse Drug Reactions During Antipsychotic Treatment Between 1993 and 2013

| | | Cardiovascular ADRs | | | | Hypotension | | Long QTc | | Arrhythmias + conduction dis. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AP imputed alone and in combination | | AP imputed alone | | AP imputed alone | | AP imputed alone | | AP imputed alone | |
| | Patients monitored | n (%) | | n (%) | | n (%) | | n (%) | | n (%) | |
| All AP | 291 510 | 376 | 0.13 | 171 | 0.06 | 37 | 0.013 | 9 | 0.003 | 34 | 0.012 |
| Amisulpride | 12 062 | 24 | (0.21) | 3 | (0.02) | 1 | (0.01) | 0 | (0.00) | 2 | (0.02) |
| Aripiprazole | 11 054 | 7 | (0.06) | 1 | (0.02) | 0 | (0.00) | 0 | (0.00) | 2 | (0.02) |
| Chlorprothixene | 12 944 | 18 | (0.15) | 5 | (0.05) | 4 | (0.03) | 0 | (0.00) | 2 | (0.02) |
| Clopenthixol+ zuclopenthixol | 7 679 | 9 | (0.12) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
| Clozapine | 34 868 | 78 | (0.23) | 44 | (0.14) | 6 | (0.02) | 2 | (0.006) | 17 | (0.05) |
| Flupentixol | 9 902 | 7 | (0.09) | 1 | (0.03) | 1 | (0.01) | 0 | (0.00) | 1 | (0.01) |
| Flupentixoldec. | 5 654 | 2 | (0.11) | 1 | (0.00) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
| Fluphenazin | 3 025 | 3 | (0.13) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
| Haloperidol | 35 075 | 50 | (0.16) | 6 | (0.02) | 2 | (0.01) | 0 | (0.00) | 4 | (0.01) |
| Haloperidol-Decanoate | 4 193 | 6 | (0.14) | 1 | (0.02) | 1 | (0.02) | 0 | (0.00) | 0 | (0.00) |
| Levomepromazine | 12 435 | 11 | (0.09) | 1 | (0.01) | 0 | (0.00) | 0 | (0.00) | 1 | (0.01) |
| Melperone | 17 661 | 18 | (0.10) | 0 | (0.01) | 0 | (0.00) | 0 | (0.00) | 1 | (0.01) |
| Olanzapine | 47 352 | 52 | (0.12) | 9 | (0.03) | 5 | (0.01) | 0 | (0.00) | 7 | (0.01) |
| Perazine | 15 270 | 14 | (0.10) | 1 | (0.01) | 1 | (0.01) | 0 | (0.00) | 1 | (0.01) |
| Pipamperone | 20 535 | 32 | (0.17) | 3 | (0.02) | 2 | (0.01) | 0 | (0.00) | 1 | (0.00) |
| Promethazine | 15 326 | 4 | (0.03) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
| Prothipendyl | 12 618 | 30 | (0.32) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
| Quetiapine | 52 370 | 76 | (0.16) | 19 | (0.05) | 7 | (0.01) | 3 | (0.006) | 12 | (0.02) |
| Risperidone | 43 016 | 48 | (0.13) | 5 | (0.02) | 3 | (0.01) | 0 | (0.00) | 4 | (0.01) |
| Risperidone LAI | 4 288 | 4 | (0.09) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
| Ziprasidone | 3 176 | 8 | (0.35) | 2 | (0.10) | 1 | (0.03) | 1 | (0.03) | 1 | (0.03) |
| Zuclopentixol-Decanoate | 3 256 | 3 | (0.09) | 1 | (0.03) | 0 | (0.00) | 0 | (0.00) | 1 | (0.03) |
| FGA high potency | 88 065 | 103 | (0.12) | 20 | (0.12) | 7 | (0.01) | 3 | (0.003) | 6 | (0.01) |
| FGA low potency | 90 963 | 107 | (0.12) | 10 | (0.12) | 7 | (0.01) | 0 | (0.00) | 2 | (0.00) |
| SGA | 191 320 | 262 | (0.14) | 99 | (0.14) | 29 | (0.02) | 8 | (0.004) | 31 | (0.02) |

Abbreviations: AP, antipsychotic; FGA, first generation antipsychotic; LAI, long acting injectable; SGA, second generation antipsychotic.

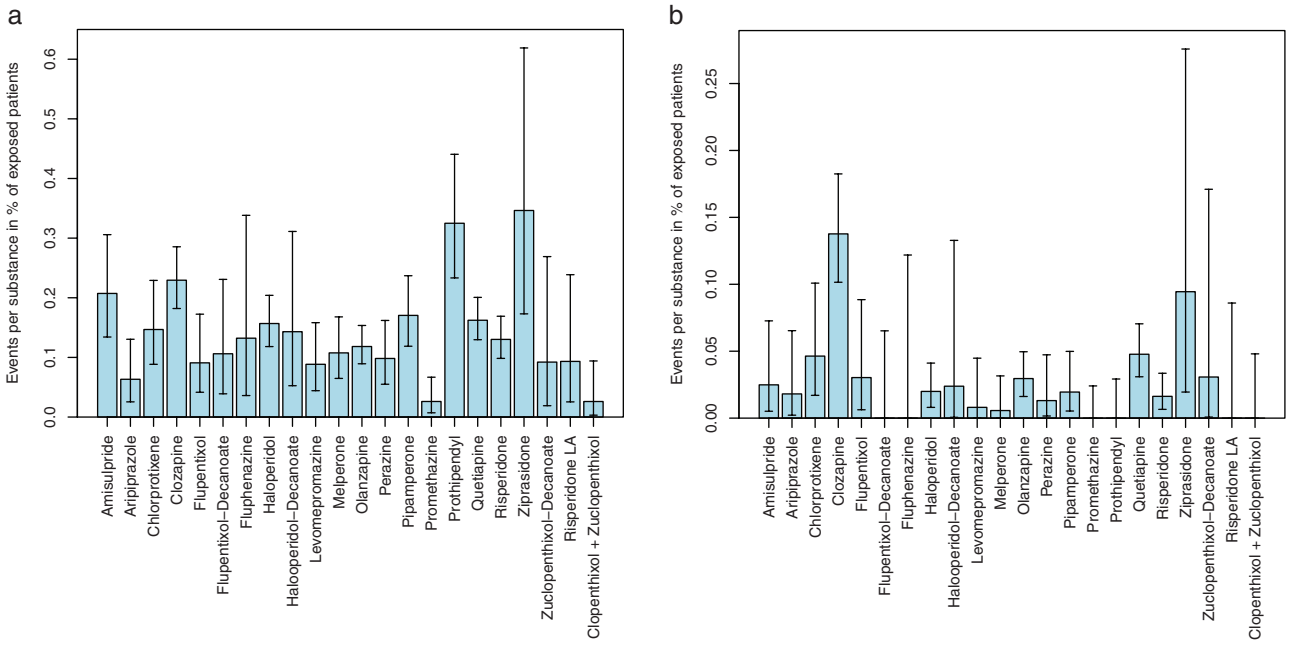


**Figure 1.** (a) Incidence rates of (%) of severe cardiovascular adverse drug reactions during antipsychotic treatment, antipsychotics (APs) imputed alone and in combination (total cases 376; Incidence rates are given with their 95% confidence intervals). Only antipsychotics with more than 3000 prescriptions are depicted. (b) Incidence rates of (%) of severe cardiovascular adverse drug reactions during antipsychotic treatment, APs imputed alone. Incidence rates are given with their 95% confidence intervals. Only antipsychotics with more than 3000 prescriptions are depicted.

**Table 3.** Types of Severe Cardiovascular Adverse Reactions with Cases (n) and Percentages of all Cardiovascular Adverse Reactions

| Severe cardiovascular ADRs | n | % |
|---|---|---|
| Orthostatic collapse | 136 | 36.2 |
| Sinustachycardia | 44 | 11.7 |
| QTc prolongation | 42 | 11.2 |
| Hypotonia | 38 | 10.1 |
| Myocarditis/pericarditis | 23 | 6.12 |
| Atrial fibrillation/atrial flutter | 16 | 4.3 |
| Ventricular extrasystoles | 17 | 4.5 |
| Sinusbradycardia | 12 | 3.1 |
| AV block | 8 | 2.1 |
| Myocardial infarction | 8 | 2.1 |
| Atrial tachycardia | 7 | 1.9 |
| Hypertonia | 6 | 1.6 |
| Cardiac arrest | 5 | 1.3 |
| Atrial extrasystoles | 4 | 1.1 |
| Ventricular tachycardia | 1 | 0.3 |
| Ventricular fibrillation | 3 | 0.8 |
| Cardiac insufficiency | 3 | 0.8 |
| Left bundle branch block | 2 | 0.5 |
| Cardiomyopathia | 1 | 0.3 |

alone, case numbers are small and no significant differences could be detected. In 64% of all cases, preexisting cardiovascular problems were present as a risk factor; still, the relation of hypotension to the imputed drugs was clear-cut in most cases (79.8%). Compared with the total population, more patients were older (37.6%, >64 years).

Six cases of hypertension were detected during AP treatment in the observation period (1.6% of all reported cardiovascular ADRs in this study). Imputed drugs were quetiapine and olanzapine alone in 2 cases each, flupentixoldecanoate in combination with clozapine and clozapine alone in 1 case each. All cases were rated as only "possible" due to likely alternative explanations.

## Arrhythmias and Conduction Disorders

A total of 117 cases of arrhythmia during treatment with APs was documented (0.04%). Cases with QTc prolongation were analyzed separately due to its specific importance in psychopharmacological drugs and are excluded here. Sinus tachycardia was most common (44 cases) followed by 16 cases of atrial fibrillation, 17 cases of ventricular extrasystoles, and 12 cases of bradycardia (see Table 3). Ziprasidone had a higher risk for these ADRs, imputed at all (0.15%) than the rate for all APs followed by amisulprid (0.10%), clozapine (0.09%), and prothipendyl (0.09%). The highest risk when imputed alone had clozapine (0.05%). For this drug, the most common ADR was sinustachycardia. For the other APs no significantly higher rate than for all APs was found (Table 2; Figure 3). In 43 of all cases with arrhythmia and conduction disorders (=37.4%), a preexisting cardiac disorder was present as a risk factor. Patients with these kind of symptoms were predominantly younger than 65 years (75.7%), similar to the total population, and only 43.5% of these cases were rated as probable (the likelihood of an alternative cause was <50%).

In 81 of the arrhythmia cases, at least 2 drugs in combination were imputed, mainly an AP with another AP (n=38 or 46.9% of all arrythmia cases), secondly with an AD (n=33 or 40.7%). Other drug combinations were with nonpsychopharmacological agents, anti-Parkinson drugs, lithium, antiepileptics, nootropics, and tranquilizers.

## QTc Interval Prolongation

As it is well-known that APs may lead to QTc interval prolongation (Nielsen et al., 2011), subanalyses on the latter were performed. QTc prolongation was assessed in 42 cases (11.2% of all cases). Atypical APs (ziprasidone, quetiapine, clozapine) were statistically significantly ($P < .001$) more often imputed alone

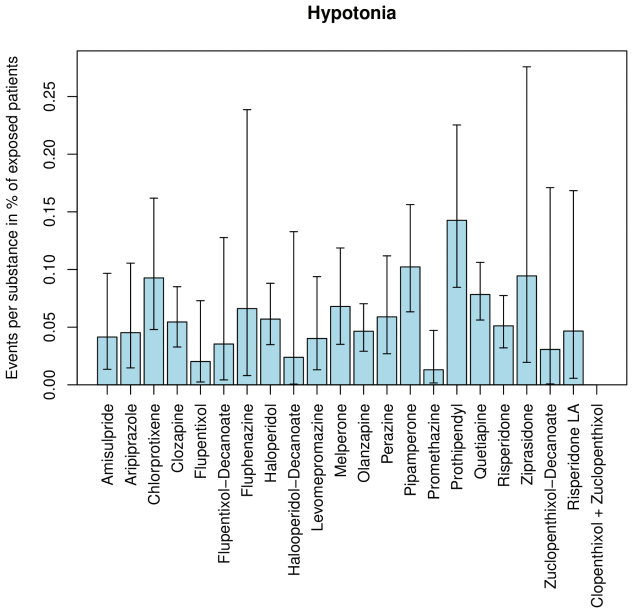


**Figure 2.** Incidence rates of hypotonia per agent in % of exposed patients; antipsychotics (APs) imputed alone and in combination; incidence rates are given with their 95% confidence intervals

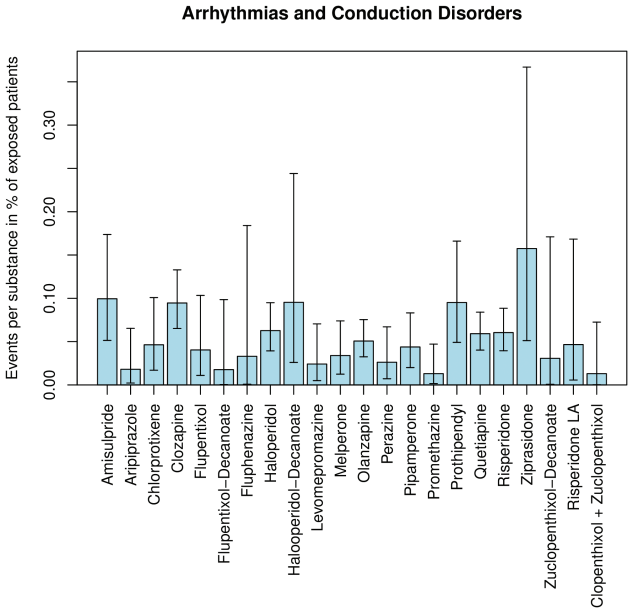


**Figure 3.** Incidence rates of arrhythmias and conduction disorders per agent in % of exposed patients; antipsychotics (APs) imputed alone and in combination; incidence rates are given with their 95% confidence intervals.

for being responsible for QTc interval prolongation than other subclasses of APs. There were no cases within first-generation high-potency agents, 3 cases within first-generation low-potency drugs (0.003%), and 8 cases within second-generation APs (0.004%). 45.2% of cases had preexisting cardiac risk factors and also here, cases were predominantly younger than 65 years (73.8%). The causal relationship was rated as probable in most cases (n = 34, 81%).

For single APs no statistical significant difference was found. The highest QTc-prolongation was 604 milliseconds with an average increased QTc of 520 milliseconds. Clinical symptoms were recorded in only 2 cases, each time with the symptom of dizziness.

In 33 cases (73.8%) a combination of at least 2 drugs was imputed, mainly of 2 APs followed by combinations of APs with ADs again, and 2 cases where the AP was combined with lithium or another nonpsychopharmacological agent.

## Myocardial Infarction, Cardial Insufficiency, and Myocarditis

Eight cases of myocardial infarction, 3 cases of cardiac insufficiency, and 23 cases of myocarditis (or pericarditis) were reported (Table 3). Clozapine was responsible for most of the myocarditis cases (in 21 cases clozapine was imputed alone, 0.006%), well-known from the literature and confirmed within our study sample. Furthermore, 1 case of cardiomyopathy, also during clozapine therapy, was reported. In only 2 myocarditis cases other APs were involved, in both cases haloperidol, once in combination with perazine and once with pipamperone.

Myocardial infarction was assessed as a possible ADR of AP treatment in AMSP only since the end of 2009 due to then-new findings in the literature about such an increased risk. Eight cases were reported in 2009–2013; in all 8 cases, cardiovascular risk factors were preexisting and 5 of these cases were fatal (see below). Haloperidol was imputed in 3 cases (all in combination with other APs), levomepromazine, clozapine, olanzapine and pipamperon were involved twice each. Clozapine, olanzapine, and pipamperon were imputed alone in 1 case each.

Three cases of heart failure were reported (0.8% of all cases), 1 case with haloperidol alone and preexisting cardiac insufficiency as risk factor, 1 case of bromperidol in combination with nortriptyline, and 1 case of olanzapine in combination with clomipramine.

In contrast to other severe symptoms, myocarditis was only associated with risk factors in 2 cases (8.7%).

## Risk Factors for and Actions After ADRs and Dose-Dependent Aspects

As already shown for most groups of CV ADR separately, the main risk factor for severe CV ADRs was a preexisting condition of the cardiovascular system (in 40.1% of all cases); other risk factors such as substance abuse (3.4%), rapid dosing (2.9%), and proneness to adverse reactions (2.9%) were rarely assessed. In 71.5% of cases the consequence after a severe drug reaction was that the agent was withdrawn. In 36.4% of the cases, drugs to counteract the ADR were prescribed. Consultation with colleagues from internal medicine was done in 25.0%, and in 24.5% patients had to be transferred to a somatic ward. Other actions were reduction of the AP medication and additional diagnostic tests. In the majority of cases (85.1%), the severe CV ADR remitted, 2.9% of cases suffered from persistent symptoms, and in 12 cases (3.1% of all cases) patients died as a consequence of the ADR.

The mean doses in milligram of AP agents when severe CV ADRs occurred were not higher than usual prescriptions in daily practice. Median dosage when clozapine was imputed alone for a CV ADR was 200 mg/day while 130 mg was used in cases associated with ziprasidon alone. In the total population, the median dosage of clozapine was 300 mg and that of ziprasidone was 120 mg. Further supplemental material on median dosages at the timepoint when CV ADRs occurred are depicted in Table 5 (supplemental material).

### Lethal CV ADRs During Antipsychotic Treatment

During the period of 1993 to 2013, 12 cases of lethal CV ADRs were assessed in AMSP during antipsychotic treatment. One 40-year old patient died from clozapine-induced myocarditis. The dosage at the time of death was 250 mg/d; in this case clozapine was imputed alone. The day before exitus the patient had a fever of 38.6°C and postmortem examination confirmed acute myocarditis. This patient did not have any known risk factors. Five cases of myocardial infarction, 2 cases with haloperidol imputed in combination with quetiapine and olanzapine, respectively, 1 case each with clozapine and quetiapine imputed alone, and 1 case with levomepromazin and clozapine, 3 cases of orthostatic hypotonia, 1 case of ventricular fibrillation, and 1 case of severe AV block (trimipramine combined with clomipramine and olanzapine were imputed in combination) as well as 1 case of cardiac arrest were reported. Orthostatic hypotonia cases were linked to combinations of 4 to 6 drugs, such as haloperidol combined with 2 beta-blockers, diuretics, prothipendyl, and melperon. In this case, the patient was 88 years old and had preexisting risk factors such as cardiac insufficiency with an implanted cardiac pace maker. Ventricular fibrillation occurred in a patient who had 15 different drugs daily. Lorazepam, oxazepam, and chlorprothixen were combined with internistic medication as well as an antibiotic (ciprofloxacin, which can potentially cause QTc-prolongation). Interestingly, as in the case where 1 patient died of orthostatic hypotonia, 2 different beta-blockers were also prescribed and imputed in combination. Nevertheless, this patient also had risk factors such as myocardial infarction several years previously as well as arterial hypertonia and diabetes mellitus. The total of 10 out of 12 cases with lethal ADRs had risk factors. The most common risk factors were adipositas and/or preexisting cardiovascular diseases.

## Discussion

The AMSP drug surveillance program has repeatedly shown links between ADRs and psychotropic agents (Letmaier et al., 2012; Spindelegger et al., 2015; Friedrich et al., 2016; Druschky et al., 2018). To our knowledge, this is the first study presenting data on antipsychotic prescriptions and severe cardiovascular ADRs within a systematic drug surveillance program.

Our descriptive study identified 376 cases of severe CV ADRs between 1993 and 2013 where 291.510 patients were exposed to antipsychotic treatment, revealing a relative frequency of 0.13%. Andor et al. (2019) just recently published their data about cardiovascular disturbances in patients with schizophrenia spectrum disorders and highlighted olanzapine long-acting injections with best outcome results in terms of patients who were untreated for a longer time. Within our dataset drawn from a much bigger sample, orally administered olanzapine showed a frequency of 0.12%, but aripiprazole (0.06%) and risperidone depot (0.09%) had even better outcome values regarding CV ADRs. The fact that aripirazole is the drug most favorable in terms of QTc-prolongation is well-known in the literature but mainly based on case reports (Polcwiartec et al., 2015) than on data from systematic drug surveillance programs and confirmed by our results. When imputed alone, clozapine showed the highest incidence rates of CV ADRs due in part to its likelihood to cause myocarditis. This clozapine-induced adverse reaction is also consistent with preexisting findings (Ronaldson et al., 2017). However, sinustachycardia and collapse were also common during clozapine therapy, which might be due to its anticholinergic action. On the other hand, Tiihonen et al., 2009 observed that clozapine was the only AP associated with significantly reduced mortality from all causes relative to perphenazine due to its reduction in suicide rates.

The CATIE study of patients with schizophrenia displayed a 2-fold prevalence of metabolic syndrome in an age- and sex-matched cohort from the general population (McEvoy et al., 2005). Antipsychotics can cause metabolic syndrome; thus, as a consequence, CV ADRs can occur. Cardiovascular disease events might be stronger associated with lifestyle factors coming along with chronic mental illness than with the pharmacology of AP agents itself. Hence, patients should be enrolled in lifestyle programs with diet improvement and frequent exercise. Furthermore, there should be more awareness regarding checkups for cardiovascular diseases and respective risk factors for patients including routine ECG monitoring and simple laboratory tests. A reduction of healthcare costs would be a possible secondary long-term benefit.

Contrary to olanzapine, ziprasidone is known for its low tendency to cause metabolic syndrome, but it must be administered with caution in patients suffering from arrhythmias or QTc prolongation (Mandrioli et al., 2015). This is confirmed by our study where ziprasidone showed the highest incidence rates for CV ADRs in terms of QTc prolongation as well as arrhythmias with 0.03% occurrence. However, within our surveillance program, ziprasidone was given only barely over 3000 times, explaining wider confidence intervals depicted in our figures.

Our data show that special emphasis has to be given to polypharmacy, especially the combination of more than 1 antipsychotic agent and even more when those compounds are combined with internistic medication. Regarding the 12 lethal cases, patients had, apart from 1 case of clozapine-induced myocarditis, imputed more than 1 drug and patients had preexisting risk factors in the majority of fatal cases. So one has to be especially careful when patients with preexisting cardiac diseases and/or obesity require a combination of more than 1 AP drug or multiple somatic drugs. Some APs antagonize alpha$_1$-receptors, which may cause orthostatical hypotonia. Nevertheless, a recently published study (Tiihonen et al., 2019) highlighted that combining aripiprazole with clozapine was associated with the lowest risk of rehospitalization and not associated with a higher rate of CV ADRs, indicating that certain types of AP combination treatment might be feasible in the treatment of schizophrenia.

Consistent with our findings, prior studies have also compared the safety of first- vs second-generation APs (Gill et al., 2005; Liperoti et al., 2009; Mehta et al., 2011; Sahlberg et al., 2015) and did not find a systematic difference between these 2 groups of APs in terms of association with major adverse cardiovascular events. The latter findings might also correspond with the fact that severe CV ADRs are more frequently associated with the underlying risk factors and often preexisting organic impairments than the nature of the antipsychotic drugs themselves. Sahlberg et al. (2015) observed prevalent cardiovascular diseases and multiple medications as risk factors as well.

Within our sample, cases of hypotonia were the most common among all severe CV ADRs. The typical and well-known CV ADR so far regarding APs is QTc prolongation; hence, there should be more awareness of the sometimes severe adverse reaction of hypotonia. Especially in terms of first-generation low-potency agents, hypotonia as a severe side effect must be taken into consideration. Further prospective and placebo-controlled investigations are needed to supplement our naturalistic observations.

### Limitations

The data obtained in this naturalistic study have several limitations because our findings reflect data from inpatients who are more likely to be severely ill and have higher antipsychotic dosages or more polypharmacy compared with outpatients. CV ADRs might be underreported and thus our incidence rates could be too low. This may be particularly true for ECG alterations, which are asymptomatic and thus may go undetected in a psychiatric inpatient ward. Furthermore, the reporting of severe adverse reactions is based on clinicians acting as individual drug monitors, so observer bias cannot be ruled out as the reporting is up to the drug monitors and their clinical experience and motivation.

The drug sertindol is very well-known in terms of cardiovascular side effects. However, probably due to this risk, sertindol was only rarely used in our data set (in only 778 patients) and is therefore not listed within our presented data as rare events cannot be reliably calculated in such a small population.

## Conclusion

Our findings suggest that in terms of newer atypical antipsychotics, aripirazole is less likely than the other antipsychotics examined in this study to precipitate CV ADRs. Inpatients with preexisting cardiovascular symptoms are significantly more at risk than individuals with healthy cardiovascular status. Thus, special attention should be given to these inpatients when prescribing antipsychotics with potential adverse effects affecting the cardiovascular system. Given the huge sample size in our observational naturalistic study, regardless its limitations, the present findings contribute significantly to existing literature on this topic and may further lead to a higher vigilance among clinicians for antipsychotic-induced cardiovascular events.

## Supplementary Materials

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

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## Statement of Interest

Since 1993 educational and research grants have been given by the following pharmaceutical companies to the 3 local non-profit associations of the AMSP: (1) Austrian companies: AESCA Pharma GmbH, AstraZeneca ÖsterreichGmbH, Boehringer Ingelheim Austria, Bristol–Myers Squibb GmbH, CSC Pharmaceuticals GmbH, Eli Lilly GmbH, Germania Pharma GmbH, GlaxoSmithKline Pharma GmbH, Janssen-Cilag Pharma GmbH, Lundbeck GmbH, Novartis Pharma GmbH, Pfizer Med Inform, Servier Austria GmbH, and Wyeth Lederle Pharma GmbH; (2) German companies: Abbott GmbH & Co. KG, AstraZeneca GmbH, Aventis Pharma Deutschland GmbH GE-O/R/N, Bayer Vital GmbH & Co. KG, Boehringer Mannheim GmbH, Bristol-Myers-Squibb, Ciba Geigy GmbH, Desitin Arzneimittel 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 Synthe´labo SA, Servier SA, SmithKlineBeecham AG, Solvay Pharma AG, Vifor SA, Wyeth AHP (Suisse) AG, and Wyeth Pharmaceuticals AG. Dr Konstantinidis received honoraria from Affiris, AstraZeneca, Novartis, Pfizer, and Servier, served as a consultant for AstraZeneca, and was a speaker for AstraZeneca, Bristol–Myers Squib, and Janssen. Drs Grohmann and Toto are involved in the project management of AMSP. Dr Toto has been a member of an advisory board for Otsouka and has received speaker´s honoraria from Janssen Cilag, Lundbeck, Otsouka and Servier. Dr Kasper has received grant/research support from Janssen Cilag Pharma GmbH, Lundbeck A/S and Schwabe; he has served as a consultant or on advisory boards for Angelini, AOP Orphan Pharmaceuticals AG, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd. and Takeda; and he has served on speakers' bureaus for Angelini, AOP Orphan Pharmaceuticals AG, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd. and Takeda. Dr Winkler has received author/lecture fees from Angelini, Lundbeck, and Medizin Medien Austria.

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