

# Hypothermia following antipsychotic drug use

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## Abstract

**Objective** Hypothermia is an adverse drug reaction (ADR) of antipsychotic drug (APD) use. Risk factors for hypothermia in ADP users are unknown. We studied which risk factors for hypothermia can be identified based on case reports.

**Method** Case reports of hypothermia in APD-users found in PUBMED or EMBASE were searched for risk factors. The WHO international database for Adverse Drug Reactions was searched for reports of hypothermia and APD use.

**Results** The literature search resulted in 32 articles containing 43 case reports. In the WHO database, 480 reports were registered of patients developing hypothermia during the use of APDs which almost equals the number of reports for hyperthermia associated with APD use ( $n=524$ ). Hypothermia risk seems to be increased in the first days following start or dose increase of APs. APs with strong 5-HT<sub>2</sub> antagonism seem to be more involved in hypothermia; 55% of hypothermia reports are for atypical antipsychotics. Schizophrenia was the most prevalent diagnosis in the case reports.

**Conclusion** Especially in admitted patients who are not able to control their own environment or physical status, frequent measurements of body temperature (with a thermometer that can measure low body temperatures) must be performed in order to detect developing hypothermia.

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## Introduction

Antipsychotic drugs (APDs) can influence thermoregulation. Even before its psychotropic properties were clear in the early 1950s, the first manufactured APD, chlorpromazine, was used to suppress compensatory responses to body cooling in surgery (artificial hibernation) [1].

The hypothermic effects of APDs seem less well known than the hyperthermic effects (e.g., malignant neuroleptic syndrome). Besides occasional case reports, little emphasis has been placed in scientific literature on hypothermia as adverse drug reaction (ADR). To our knowledge, a review of all reported and published cases of antipsychotic associated hypothermia has not yet been published.

## Methods

The WHO international database for Adverse Drug Reactions was searched for reports of hypothermia and APD use (ATC-code N05A, with exclusion of lithium). The data in the database are collected from 77 countries participating in the WHO Program for International Drug Monitoring. This database comprises more than 3.5 million case reports, to which around 50,000 new reports are added quarterly. The relationship between the APD and hypothermia is evaluated by calculating the Reporting Odds Ratios (RORs) and 95% confidence intervals (95% CI) in a case/non-case design. The ROR compares the frequency of the reported ADR for a certain drug with the frequency of reports of that adverse drug reaction for all other drugs in the database. Reports

concerning hypothermia were considered as cases, all other reports as non-cases. Index reports included all reports on an APD (ATC code beginning with N05A, with exclusion of lithium), all other reports were controls. When the number of reports of hypothermia in association with the APD is high and the number of reports of hypothermia in association with other drugs is low, ROR will be high. This also happens when the number of reports of other ADRs in association with the APD is low and the number of reports of other ADRs in association with other drugs is low. Since

the vast majority of cases in the WHO database do not contain any details on indication of drug use, start and/or end dates and outcome, these factors cannot be analyzed with data from the WHO database. To get more information regarding characteristics of patients developing hypothermia during APD use, we performed a literature search in Medline and Embase for case reports with search terms “(antipsychotic OR neuroleptic) AND (hypothermia OR body temperature regulation), with no selection on date or language. From these articles, we searched the references

**Table 1** Antipsychotic drugs and hypothermia: reports from the WHO database

Antipsychotic drug	Number of reports for hypothermia	Number of reports for any ADR with this drug	Reported OR (CI) <sup>a</sup> for ADRs with $\geq 3$ reports
<b>Tioxanthenes</b>			
Zuclopenthixol	13	1094	15.88 (9.18–27.47)
Flupenthixol	6	1677	4.73 (2.12–10.55)
Chlorprothixen	4	502	10.58 (3.95–28.31)
Tiotixene	3	904	4.38 (1.41–13.62)
Clopenthixol	2	293	-
<b>Phenothiazines</b>			
Thioridazine	23	4436	6.90 (4.57–10.41)
Chlorpromazine	16	6182	3.43 (2.09–5.60)
Levomepromazine	11	2348	6.21 (3.43–11.24)
Cyamemazine	9	1197	9.99 (5.18–19.27)
Periciazine	8	430	25.00 (12.41–50.36)
Pipothiazine	3	197	20.36 (6.50–63.71)
Fluphenazine	3	2656	1.49 (0.48–4.62)
Trifluoperazine	3	1895	2.09 (0.67–6.48)
Perphenazine	2	1522	-
Prochlorperazine	2	4451	-
Promazine	2	307	-
Mesoridazine	1	215	-
<b>Butyrofenones</b>			
Haloperidol	32	10543	6.21 (3.43–11.24)
Pipamperone	10	546	24.62 (13.16–46.07)
Droperidol	2	1178	-
Benperidol	1	146	-
<b>Benzamides</b>			
Tiapride	5	596	11.14 (4.62–26.89)
Sulpiride	4	1828	2.89 (1.08–7.70)
Amisulpiride	1	1514	-
Sultopride	1	72	-
<b>Others</b>			
Loxapine	4	928	5.70 (2.13–15.23)
Pimozide	3	628	6.31 (2.03–19.65)
Zotepine	2	260	-
Prothipendyl	1	93	-
Penfluridol	1	58	-
<b>Atypical</b>			
Risperidone	129	18431	9.65 (8.09–11.52)
Clozapine	68	44255	2.05 (1.61–2.61)
Olanzapine	44	16090	3.65 (2.71–4.91)
Quetiapine	21	5374	5.19 (3.38–7.98)
Aripiprazole	11	4566	3.18 (1.76–5.76)
Ziprasidone	8	2963	3.57 (1.78–7.15)

<sup>a</sup> ROR = (a/c) / (b/d); (a = no. of reports of adverse drug reaction with suspected drug;

b = no. of reports of adverse drug reaction in total database; c = no. of reports regarding the suspected drug in database; d = total no. of reports in database). ROR is only calculated for APDs with three or more reports

for missing articles. Two reviewers judged all case reports. All relevant case reports were studied for patient, drug and environmental characteristics.

## Results

In the WHO database, in January 2007, 480 reports were registered of patients developing hypothermia during the use of APDs. Characteristics of these reports are presented in Table 1. In the same period, 524 reports of hyperthermia associated with antipsychotic drug use were registered. Based on the reports, no specific pharmacological subgroup can be associated with an increased risk for hypothermia. Atypical antipsychotics are responsible for 55% of the reports, but this is mainly attributable to risperidone. Risperidone alone was responsible for 27% of all reports. A remarkable high association is found for pipamperone (ROR:24.62; 95% CI 13.16–46.07), an antipsychotic drug mainly used in Europe.

The literature search resulted in 32 articles containing 43 case reports (December 2006) [3–34] from which characteristics are summarized in Table 2. Hypothermia following antipsychotic drug use is not associated with a specific age group. Reported ages vary from 0 to 90 years. In most cases, hypothermia is detected shortly following the start or dose increase of an antipsychotic drug. Most patients suffered from schizophrenia.

**Table 2** Characteristics of cases with hypothermia following antipsychotic drug use in literature (43 case reports, 46 episodes)

Characteristics	Data
Male	41%
Age: mean (SD)	49 (23.0)
	Range 0–90 years
Reported body temperature: mean (SD)	32,6°C (2.7)
	Range 20.0–36.1°C
Diagnosis known ( <i>n</i> =35)	
Schizophrenia	51%
Mental retardation	11%
Bipolar disorder	11%
Dementia	11%
Drug change Start or dose increase	80%
No change	16%
Interval drug change detection hypothermia	
<2 days	57%
2–7 days	16%
Outcome death	4%
ICU admission	24%
Hospitalization (incl. prolonged)	69%

## Discussion

Hypothermia in patients using an APD is a serious, unpredictable, type B adverse event frequently leading to hospital and ICU admission and sometimes even to death. Some authors have even suggested that a substantial proportion of unexplained deaths should be attributed to antipsychotic-induced hypothermia [3, 35]. No single sufficient cause for hypothermia can be found in case reports. First, drug-receptor profile may play a role. Serotonin is associated with thermoregulation and APDs with a stronger affinity for the 5-HT<sub>2a</sub> receptor than for the D<sub>2</sub>-receptor (pipamperone, the atypical APDs) seem to be associated with hypothermia. The high association for relatively new drugs, like the atypical APDs, can partially be explained by reporting bias (reporting incidence for adverse drug effects is higher for new drugs and tends to decline in time; the so-called Weber-effect), but the high number of reports for risperidone should keep clinicians alert. Blocking alpha<sub>2</sub>-adrenergic receptors (e.g., chlorpromazine, risperidone, clozapine, thioridazine) may also increase the hypothermic effect, by inhibiting peripheral responses to cooling (vasoconstriction and shivering). Next to this receptor profile, many patient-bound factors must be considered. Patients with pre-existing brain damage may be more susceptible to hypothermic effects. The pre-optic anterior hypothalamic region regulates body temperature. Animal studies show that lesions of this region give a hypothermic response following administration of an APD [36, 37]. In patients with multiple sclerosis, hypothermia is also associated with thalamic lesions [38]. Studies in schizophrenic patients show that core temperature decreases following the administration of APDs [39, 40]. Our search shows a predominance of case reports for schizophrenic patients and little for other frequent APD user groups like demented or delirious elderly. In schizophrenia, thermal regulation is altered. This may be explained by changes in neurotensine levels in schizophrenia. Neurotensine (NT) is one of the most important thermoregulatory peptides that also plays a role in the antipsychotic actions of APDs. In schizophrenic patients, NT concentration in cerebro-spinal fluid (CSF) is low and will be normalized following antipsychotic drug use [41]. The hypothermic reaction is also dependent on ambient temperature. In animal studies, APD administration at ambient temperatures below 22°C led to hypothermia, whereas APD administration in a room temperature of 29°C gave no thermal response and at 32°C an increase in rectal temperature [41, 42]. Normally, a cold environment will result in behavior aimed at protection against the cold (taking extra blankets or clothes). APDs, however, will induce apathy and indifference, resulting in unawareness of developing hypothermia. Since some case reports also mention the co-existence of infections at the

time of development of hypothermia, this may also play a role in the dysregulation of thermal homeostasis.

There is an ongoing discussion concerning the value of case reports and spontaneous reports in the field of drug safety. There can be no discussion that pharmacodiligence requires prospective studies, access to regulatory filings for controlled and monitored use of drugs, and some sense of relative potency for comparison between different drug entities. However, large cohorts are needed for the detection and analysis of type B reactions. Since these data are lacking, case and spontaneous reports by alert clinicians must be analyzed [43]. The outcome of such an analysis cannot be seen as solid evidence, but can help to get more insight in the adverse drug reaction (ADR). The use of measures like ROR and disproportionality can help to detect drugs with an increased association with an ADR. A statistically significant ROR may be indicative of a higher risk for that particular event during the use of a specific medication, but is never conclusive for the actual existence of a causal relation [2].

The results of this study should alert physicians of the risk of hypothermia in psychiatric patients using APDs. There seems to be no direct relation between stable drug dose and the ADR; the period shortly after starting the APD or dose increase seems to be the high risk period. Often, drug changes are indicated by behavioral problems also leading to separation or isolation of the patient. In the case of separation, patients will be dressed lightly and, even at normal room temperature, can cool down easily. In these cases, the patient's body temperature should be monitored daily (with a thermometer that can measure low body temperatures). Also, every change in behaviour or comorbidity (e.g., infections) should be a warning sign to look for hypothermia.

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