

# Serious Adverse Drug Reactions to Antipsychotics in Minors with Multiple Disabilities: Preventability and Potential Cost Savings by Therapeutic Drug Monitoring



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## ABSTRACT

**Introduction** Children and adolescents with multiple disabilities and mental disorders (CAMD) are frequently treated with antipsychotic drugs. However, CAMD are particularly susceptible to serious adverse drug reactions (sADRs). This retrospective study examined the frequency of sADRs to antipsychotics in CAMD. Further, the potential preventability of these sADRs through therapeutic drug monitoring (TDM) and the potential socio-economic benefits of TDM were explored.

**Methods** Routine clinical data of all patients treated at a specialized psychiatric clinic for CAMD between January 2017 and December 2018 were retrospectively examined. Data on the occurrence of sADRs (definition according to the European Medicines Agency), their causality with antipsychotics, as well as their preventability (Schumock criteria) were extracted from patient files. The prolongation of the hospital stay due to sADRs was calculated, and the cost savings were estimated if TDM had been applied. The data were based on a subsample of the KiD-Safe project, supported by the Innovation Fund of the Joint Federal Committee, grant number 01NVF16021.

**Results** One hundred two CAMD who were administered at least one antipsychotic drug during inpatient treatment were identified. Of these patients, 22 (21.6%) sADRs with a possible causal relationship with the antipsychotic treatment were documented. Eleven sADRs (50%) could potentially have been prevented through TDM. Mitigating sADRs through TDM likely would have prevented prolonged hospital stays and thus conferred considerable savings for health insurance companies.

**Discussion** The routine implementation of TDM is urgently recommended for antipsychotic treatment in CAMD to increase drug therapy safety.

## Introduction

Children and adolescents with multiple disabilities have a 3 to 4 times higher prevalence of mental disorders compared to children without disabilities [1]. Treatment of mental disorders in these patients is challenging and often involves psychopharmacotherapy. Antipsychotic drugs are commonly prescribed 'off-label' for indications such as schizophrenia or challenging behaviors, like aggression [2, 3], which is associated with an increased risk of adverse drug reactions (ADRs) [3, 4]. Antipsychotics generally show an unfavorable profile of ADRs with an increased risk in children and adolescents compared to adults for endocrine, metabolic as well as neurological complications (such as extrapyramidal motor symptoms, EPS) [5–7]. Children and adolescents with multiple disabilities and mental disorders (CAMD) are even more vulnerable to ADRs due to frequent comorbid somatic diseases such as epilepsy or congenital heart defects [8]. Medications for those somatic conditions can, in turn, increase the risk of ADRs due to drug interactions. Moreover, in this group of ADRs, the efficacy and tolerability of medications are more difficult to assess due to the communicative impairments of the patients, which can lead to suboptimal dosing or polypharmacy.

Serious ADRs (sADRs) are defined here as fatal or life-threatening adverse reactions that require hospitalization or the prolongation of existing hospitalization, or lead to persistent or significant disability [9]. Due to the suspected high prevalence of (s)ADRs under antipsychotic treatment in CAMD, psychopharmacological therapy surveillance is important.

One potential tool to prevent (s)ADRs is therapeutic drug monitoring (TDM). TDM determines whether drug levels are within a defined drug-specific therapeutic reference range, outside of which ADRs are more likely to occur, or whether the drug is not efficacious. This instrument of pharmacovigilance is well-established in adult psychiatry [10, 11]. However, there are still no age-specific therapeutic reference ranges for minors [10] despite ongoing research [12, 13]. Until age- and indication-specific therapeutic ranges are defined for all psychotropic drugs, TDM is useful in child and adolescent psychiatric patients to identify 'the therapeutic window of a patient, to reduce the risk of dose-dependent ADRs, control drug adherence, and in cases of polypharmacy [10, 13, 14]. The detailed, specific indications and practical guidelines for TDM can be found elsewhere [10, 13].

Studies with adult patients show that TDM is also useful from a health-economic point of view, as it can increase therapy efficiency and, in antipsychotic treatment, in particular, safety [15–19] and thus save costs [20, 21].

This retrospective study aimed to examine the frequency of sADRs in CAMD treated with antipsychotics and the potential preventability of these sADRs through TDM. Furthermore, the prolongation of the hospital stay due to sADRs was estimated, as well as the potential cost savings if TDM had been applied.

## Methods

### Study design

This monocentric, retrospective clinical cohort study was based on a child and adolescent psychiatric subsample (health care data of

a special clinic for CAMD) of the KiDSafe project, which was approved by the Ethics Committee of the University of Wuerzburg (245/18). The data of the overall sample has been submitted elsewhere. KiDSafe was funded by the Innovation Fund of the Joint Federal Committee (grant number 01NVF16021). The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013). No written informed parental consent was obtained because the routine clinical data were analyzed retrospectively and anonymized before analysis. Approval was obtained by the local data protection officer prior to data extraction.

### Study population

The study was carried out in the special clinic for CAMD, associated with the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy of a University Hospital. Patients were included in this study if they were admitted to the special clinic between 2017 and 2018 and were prescribed an antipsychotic drug during their stay. For this reason, patients' electronic medical records were screened. The study population included patients who were already receiving (multiple) antipsychotic medication on admission, as well as patients who had an antipsychotic (re)started, switched, or had their dose changed during the inpatient stay. Patient characteristics (age, sex), (main) psychiatric diagnosis, and all psychotropic drugs administered were recorded. Cognitive ability was determined with standardized tests or were based on records or clinical impressions.

### Frequency of serious adverse drug reactions

A checklist based on the Pediatric Adverse Event Rating Scale (PAERS) [22] was created. For all patients receiving antipsychotics, discharge letters, consultation reports, inpatient documentation, and clinical test reports (vital signs, laboratory parameters, ECG, and EEG) were reviewed to identify instances of possible serious adverse events with a possible causal relationship to the drug (considered as sADR) as defined according to EMA [9] and WHO [23]. A 'possible causal relationship' describes a temporal relationship between the drug and the adverse event without ruling out that an underlying disease or other medication may be responsible for the event.

### Potential preventability of serious adverse drug reactions

The Schumock score [24] was used to assess the potential preventability of a sADR (► **Table 1**). The sequence of events from prescription to administration to medication intake was assessed for errors according to seven criteria. If any of these criteria was fulfilled, the sADR was considered preventable. One medication could fulfill more than one criterion of preventability. Criterion 3 was considered fulfilled if no TDM was performed for the antipsychotic suspected to be the cause of the sADR. In this case, the sADR was classified as 'potentially preventable through TDM.'

Estimation of treatment prolongation due to sADRs and potential cost savings from their prevention

The 'prolongation of the hospital stay' due to the sADR was measured as the duration (in days) until the symptoms of the sADRs subsided after stopping the medication or reducing the dose. This was determined from the case documentation.

► **Table 1** Schumock score for assessing the preventability of adverse drug reactions [24].

Criterion number	Question	Answer
1	Was the drug involved in the ADR <i>not</i> considered appropriate for the patient's clinical condition?	yes/no
2	Was the dose, route, and frequency of administration not appropriate for the patient's age, weight, and disease state?	yes/no
3	<b>Was required therapeutic drug monitoring or other necessary laboratory tests not performed?</b>	yes/no
4	Was there a history of allergy or previous reactions to the drug?	yes/no
5	Was a drug interaction involved in the reaction?	yes/no
6	Was a toxic serum drug level documented?	yes/no
7	Was poor compliance involved in the reaction?	yes/no

To estimate the cost-saving potential by preventing sADRs through TDM, we calculated the 'prolongation of the hospital stay' of the patients in whom sADRs occurred and no TDM was performed (Schumock Criterion 3). Saved costs were calculated by multiplying those prolonged days by the average base daily rate of the special clinic per patient based on the current German flat-rate remuneration system for psychiatry and psychosomatics (at least 400 €/day).

## Data analysis

Statistical analysis was performed using SPSS version 26. Descriptive results are reported with mean, +/− standard deviation (SD), and range.

## Results

### Patient characteristics

During the survey period, 124 CAMD (65% male, 69% ≥ 12 years) were treated within the framework of a multimodal treatment concept. One hundred two (82%) were administered at least one antipsychotic drug in monotherapy or polypharmacy during inpatient treatment. The characteristics of those patients are mentioned in ► **Table 2**. The most frequent diagnoses were developmental disorders (ICD-10 F8). The vast majority of patients (91%) had mild to moderate intellectual disabilities. The total number of antipsychotic prescriptions in the 102 children and adolescents was 273. Substances used most often were pipamperone (n = 56), risperidone (n = 48) and aripiprazole (n = 44).

### Frequency of serious adverse drug reactions

Among CAMD, 21.6% (n = 22 out of 102), who were treated with one or more antipsychotic drugs experienced sADRs. ► **Table 3** shows the severity criterion according to EMA [9]. In 16 cases, the ADR prolonged the patient's inpatient stay, and in four cases, the

► **Table 2** Characteristics of patients with multiple disabilities and mental disorders treated with antipsychotics (n = 102).

	m ± SD
<b>Age (years)</b>	13.4 ± 3.5
< 12 years, n = 33 (32%)	
≥ 12 years, n = 69 (68%)	
<b>IQ (n = 56)</b>	54.1 ± 12.7
Normal range (85–114): n = 1	93 ± 0
Borderline intellectual functioning (70–84): n = 2	74.0 ± 2.8
Mild intellectual disability (50–69): n = 33	60.0 ± 5.2
Moderate intellectual disability (35–49): n = 18	41.4 ± 5.0
Severe intellectual disability (20–34): n = 2	30 ± 0
	<b>n</b>
<b>Sex</b>	
Male	68
Female	34
<b>Main psychiatric diagnosis (ICD-10)</b>	
Organic, including symptomatic mental disorders (F0)	1
Schizophrenia spectrum disorders (F2)	6
Affective disorders (F3)	2
Neurotic, stress, and somatoform disorders (F4)	3
Behavioral disorders with physical disorders and factors (F5)	2
Personality and behavioral disorders (F6)	3
Intelligence disorder (F7)	4
Developmental disorders (F8)	47
Behavioral and emotional disorders with onset in childhood and Adolescence (F9)	34
<b>Diagnosis of epilepsy</b>	22
<b>Total number of antipsychotic prescriptions</b>	273
Pipamperone (on-demand medication)	56
Risperidone	48
Aripiprazole	44
Melperone (on-demand medication)	32
Zuclopenthixol	27
Chlorprothixen (on-demand medication)	19
Quetiapine	16
Levomepromazine (on-demand medication)	11
Haloperidol	8
Olanzapine	8
Clozapine	2
Thioridazine	2
Tiapride	1

m = mean, SD = standard deviation, IQ = intelligence quotient.

ADR resulted in the patient's admission. Two sADRs were life-threatening, and one sADR was lethal.

Of sADRs, 95% (n = 21) were somatic symptoms, and one was a psychiatric event. QTc prolongation and EPS were the most frequent sADR. The frequency of the affected organ systems and the type of sADR are shown in ► **Table 3**.

► **Table 3** Description of potentially preventable and nonpreventable serious adverse drug reactions (sADRs) on antipsychotic medication and duration.

Patient information (age; main psychiatric/somatic disorders (ICD-10))	Type of sADR	Description of sADR	Severity criterion according to EMA [9]	Suspected antipsychotic(s) (+other suspected psychotropic drug)	Criterion for the preventability of the sADR, according to Schumock [24]	Prolongation of treatment (n=100)
8 years; PDD (F8), MR (F71)	Cardio-vascular ADRs	QTc:460 ms	<b>Prolonged stay</b>	Zuclopendthixol, (Amphetamine)	1 3	8
17 years; EBD (F9), MR (F70), obesity (E66)		QTc:480 ms	<b>Prolonged stay</b>	Zuclopendthixol, Quetiapine	1 3 5	19
12 years; EBD (F9), MR (F70), congenital malformations of the heart (Q24), epilepsy (G40), obesity (E66)		QTc:550 ms	fatal	Aripiprazole, (Guanfacine)	3 5	-
15 years; PDD (F8), MR (F72)		QTc:529 ms	<b>Prolonged stay</b>	Aripiprazole, Zuclopendthixol, Pipamperone	2 3 5	18
16 years; schizophrenia (F2), MR (F70)		QTc:539 ms	Admission to hospital	Clozapine	6	
16 years; PDD (F8), MR (F71)		QTc:479 ms	Prolonged stay	Aripiprazole, Melperone, Risperidone	2 5	
14 years; PDD (F8), MR (F70), chromosomal abnormality (Q99), disorder of ear (H9)	EPS	Rigor, tremor, akinesia, gaze spasm, tongue or gullet spasm, akathisia, myoclonus, gait disturbance.	<b>Prolonged stay</b>	Aripiprazole	2 3	11
16 years; PDD (F8), MR (F72), microcephaly (Q02), disorders of refraction and accommodation (H52)			Prolonged stay	Quetiapine, Aripiprazole, Melperone, (Lorazepam, Melatonin)	1 2 5	
19 years; schizophrenia (F2), MR (F71), Di George syndrome (D82), scoliosis (M41)			<b>Prolonged stay</b>	Haloperidol	3	12
15 years; EBD (F9), MR (F70), congenital malformations of heart (Q24)			<b>Prolonged stay</b>	Zuclopendthixol	2 3	2
15 years; adjustment disorder (F4), MR (F70), Di George syndrome (D82), epilepsy (G40), congenital malformations of cardiac septa (Q21)			Prolonged stay	Risperidone, Melperone	1 5	
13 years; PDD (F8), MR (F71), disorders related to short gestation and low birth weight (P07), microcephaly (Q02), spastic diplegic cerebral palsy (G80), cerebral cysts (G93)			<b>Prolonged stay</b>	Zuclopendthixol	2 3	4

► Table 3 Continued

Patient information (age; main psychiatric/somatic disorders (ICD-10))	Type of sADR	Description of sADR	Severity criterion according to EMA [9]	Suspected antipsychotic(s) (+ other suspected psychotropic drug)	Criterion for the preventability of the sADR, according to Schumock [24]	Prolongation of treatment (n = 100)
17 years; MR (F71), schizophrenia (F2)	Epileptic seizure	Epileptic seizure	Prolonged stay	Clozapine, Aripiprazole	5	
14 years; EBD (F9), MR (F70), disorders of refraction and accommodation (H52)	Gastrointestinal ADR	Nausea, vomiting, abdominal pain with diarrhea	Admission to hospital	Quetiapine, (+ Sertraline)	1	
11 years; EBD (F9), MR (F70)			Prolonged stay	Aripiprazole	2	
14 years; EBD (F9), MR (F70), epilepsy (G40)		Increased salivation	<b>Prolonged stay</b>	Thioridazine, Risperidone	1	19
16 years; habit and impulse disorders (F6), MR (F7), epilepsy (G40)			Prolonged stay	Pipamperone, Melperone, Aripiprazole	3	
8 years; EBD (F9), MR (F71), abnormal results of function studies of the central nervous system (EEG) (R94)			<b>Prolonged stay</b>	Zuclophenixol, (Valproate),	1	7
17 years; schizophrenia (F2), MR (F70), epilepsy (G40), microcephaly (Q02), chromosomal abnormality (Q99), atrioventricular and right fascicular block (I44, I45)	Weight change	Weight gain (> 10 kg)	Prolonged stay	Olanzapine	not avoidable	
17 years; habit and impulse disorders (F6), MR (F72), drug-induced obesity (E66), congenital malformations of cardiac septa (Q21)	Blood count change	Liver value increase	Admission to hospital	Pipamperone, Risperidone	5	
14 years; MR (F71), other congenital malformations of the heart (Q24)		Aplastic anemia	Admission to hospital	Zuclophenixol, Melperone, Tiapride, (Lamotrigine)	1	
11 years; PDD (F8), MR (F71), cerebral cysts (G93.0)	Psychiatric ADR	(auto-) aggression	life-threatening	Aripiprazole, (Oxcarbazepine)	3	
			life-threatening		5	
					1	

ICD-10 = International Statistical Classification of Diseases and Related Health Problems 10th Revision; EMA = European Medicine Agency, (s)ADR = (serious) adverse drug reaction, EPS: extrapyramidal symptoms, PDD: pervasive developmental disorder, MR: mental retardation, EBD: emotional and behavioral disorders, QTc: frequency-corrected QT interval according to Bazett.

## Antipsychotics linked to suspected serious adverse drug reactions

One hundred two patients received a total of 273 antipsychotic drug prescriptions. For 37 prescriptions, sADRs were reported (► **Table 2**). The drug with the highest absolute number of suspected sADRs was the third-generation antipsychotic aripiprazole (9 sADRs in 44 patients on aripiprazole; 20.5%). Proportionately, the first-generation antipsychotic zuclopenthixol was most frequently associated with sADRs (7 sADRs in 27 patients on zuclopenthixol; 25.9%). Fifteen Patients with sADR (68.2%) were administered more than one psychotropic drug.

## Potential preventability of serious adverse drug reactions

According to the Schumock score, 95.5% (n = 21) of the sADRs (n = 22) were potentially preventable (see ► **Table 3**). In 11 of these cases, no TDM was performed (criterion 3). In 11 cases, avoidance of the interaction with co-medication could have prevented the sADR (criterion 5). In 10 cases, the antipsychotic drug linked to the sADR was not considered appropriate for the clinical condition of the patient (criterion 1). A dosing error was observed in seven patients (criterion 2). One patient showed a too-high serum level (criterion 6).

## Prolongation of treatment by serious adverse drug reactions and estimation of cost savings due to therapeutic drug monitoring

For 16 patients, prolongation of the hospital stay due to a sADR was documented. In total, 246 'prolongation days' until the complete resolution of sADR symptoms were documented. For 11 of those patients, sADRs were judged as 'potentially preventable through TDM' based on Schumock criterion 3 (n = 11). For nine patients, the prolongation of their stay resulted from a sADR, which could have been prevented with TDM, with a total of 100 prolongation days. Our findings indicate that the use of TDM could have reduced patient stays by 100 days for a total of nine patients (with 9 of 22 sADR recorded; 40.9%), resulting in potential savings of approximately €40,000.

## Discussion

### Frequency and nature of serious adverse drug reactions under antipsychotic treatment

In our study, around 20% of CAMD treated with antipsychotics for various psychiatric disorders suffered at least one sADR. This reflects the high vulnerability of ADRs in this group of pediatric patients and underlines the need for highly standardized therapy surveillance.

EPS and QTc prolongation were the most frequently observed sADRs. Interestingly, in the TDM Vigil study [25], psychiatric (not somatic) sADRs were most frequently reported. In our sample, psychiatric sADRs were very rare. One possible explanation is that psychiatric sADRs are harder to recognize in patients with multiple disabilities due to impairments of those patients in introspection and communication. Furthermore, in contrast to the prospective TDM vigil study, our investigation relied on retrospective excerpts from

routine documentation. It is also possible that psychiatric ADRs are documented less frequently since they may be attributed to the underlying disability. It is, however, likely that CAMD are more prone to somatic ADRs [8].

The first-generation antipsychotic zuclopenthixol, which is not licensed for pediatric use, was most frequently associated with a sADR relative to prescription frequency. Notably, conducting TDM for this substance was not possible in our laboratory during the observation period, which may also have contributed to the high rate of sADR under zuclopenthixol treatment.

The purely descriptive results of our study suggest that typical antipsychotics, like zuclopenthixol, may be unsuitable for pediatric patients, and second-generation atypical antipsychotics may be preferable, as recommended in guidelines [26]. However, this retrospective study was not suitable or intended to investigate the tolerability profile of different antipsychotics. Further prospective studies are needed to confirm the results.

### Assessment of preventability of serious adverse drug reactions by therapeutic drug monitoring

Eleven patients who experienced a sADR did not undergo TDM. TDM is based on the assumption that there is a relationship between serum concentration and the clinical effects of a drug. The upper limit of the therapeutic range, if exceeded, warns of the occurrence of ADRs. However, TDM in pediatric patients is limited by the fact that reference ranges are defined for adults and are mostly not validated for children and adolescents and their specific indications. Nevertheless, that TDM with the knowledge on adult reference ranges is valuable also in minors shows a representative example of our sample: A 16-year-old patient with schizophrenia (ICD-10 F2) was treated with clozapine (750 mg/day) and suffered from a prolonged QTc (► **Table 3**). The measured clozapine drug level (796 ng/mL) lay clearly above the reference range for adults (300–600 ng/mL) [21]. The dose was reduced, and the patient recovered. An association between serum concentration and ADRs has been demonstrated for clozapine [27, 28], haloperidol [29], olanzapine [30, 31], risperidone [32, 33], and ziprasidone [34], for example.

Age- or indication-specific therapeutic reference ranges for children and adolescents have also been proposed for antipsychotics, e. g., for tiapride in the treatment of tic disorders [35], risperidone in the treatment of children and adolescents with impulsive-aggressive behavior [36] and schizophrenia, and pipamperone in children and adolescents with conduct disorder [37]. No TDM studies have been conducted specifically for CAMD. This critical topic warrants further research.

Sixty-eight percent of patients with documented sADRs were being treated polypharmacologically. Polypharmacology is the only indication for TDM specifically recommended for CAMD in the current guidelines [26]. In four patients, both Schumock criterion 5 (interaction) and criterion 3 (no TDM) were fulfilled. For example, a QTc prolongation occurred in a 15-year-old patient treated with zuclopenthixol, aripiprazole, and pipamperone (► **Table 3**). As all these antipsychotics have the potential to cause concentration-dependent QTc-prolongation [38], and a TDM would have been strongly indicated. Our results confirm the importance of TDM if polypharmacy is necessary.

## Cost-saving potential of therapeutic drug monitoring

In addition to enhancing patient safety and treatment efficacy, TDM has the potential to reduce unnecessary healthcare costs. Shortening hospital stays through TDM-guided antidepressant therapy has previously been shown in studies with adult patients [20, 39]. The estimation in our study supports the premise that TDM has significant cost-saving potential by reducing the frequency of sADRs and therefore preventing prolonged inpatient treatment in this particular patient population. Additionally, other indications for TDM, e. g., problems with adherence or relapse prevention [16, 17], have great potential for savings. The potential cost savings calculated in this study are approximately €40,000 for a 2-year survey period, including 102 CAMD on antipsychotics. Therefore, the use of TDM can optimize pharmacotherapy to prevent and shorten inpatient stays. This health-economic benefit becomes even clearer when the costs of a serum concentration determination (25€ for physicians in Germany) are compared with the daily rate of inpatient psychiatric treatment, which is more than 15 times higher in most specialized child and adolescent psychiatric clinics.

## Limitations

The results of this study must be evaluated in the context of the limitations of a retrospective study. All data were based on the available routine case documentation. Thus, poor or biased documentation may have affected results. However, the department has previously participated in pharmacovigilance drug RCTs (TDM-VIGIL), having substantially improved the standards for documentation on drug treatment. Furthermore, as this was a monocentric study and only prescription patterns and drug monitoring of one highly specialized clinic were evaluated. Thus, these results may not be generalizable to other settings.

The causal relationship between sADR and antipsychotic treatment was assessed using WHO criteria [23]. None of the cases had been classified as a 'probable' or 'certain' causal relationship. Therefore, most cases had only a 'possible' causal relationship to antipsychotic therapy. Accordingly, other causes (e. g., severe chronic somatic disorders) could also be responsible for the occurrence of severe events. However, the assessment using WHO criteria is a standardized process, which is also used in pharmacovigilance practice in the EU. In some cases, more than one antipsychotic or other psychotropic drugs were suspected of causing the sADR.

It is also not known whether TDM could have actually prevented sADRs. We do not possess information on whether the reason for the sADR was an overdose or a drug interaction. A further limitation is the lack of age- and indication-specific therapeutic reference ranges.

Regarding the role of TDM in the prolongation of stays and cost-saving potential, results have to be interpreted carefully. The duration of inpatient stay may also have depended on other factors not recorded in this study (e. g., symptom aggravation irrespective of medication). Also, in some cases, TDM was not the only fulfilled criterion of preventability. So, preventability by TDM and, thus, the cost-saving potential of TDM may have been overestimated. Moreover, the calculation of the cost savings was based only on rounded rough estimates. However, the lowest estimated value for the special clinic's average base daily rate per patient was used. Nowa-

days, the daily rates are already significantly higher. In addition, there are still the costs of TDM to consider, which are, however, comparatively low.

## Conclusion

sADRs in CAMD are frequent and a reason for concern. Many of those sADRs may be potentially preventable through TDM. It is therefore recommended that TDM is implemented in daily clinical practice for this particularly vulnerable group of minors in order to increase medication safety while reducing healthcare costs. Prospective studies are needed to confirm our results regarding the frequency and type of sADRs as well as the benefits of TDM.

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## Conflict of Interest

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