

Clinico-toxicological assessment of atypical antipsychotics

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1. Objective

Since the introduction of clozapine - the prototype of atypical antipsychotics - especially in the last ten years new antipsychotics came into the market, be aimed at efficacy against negative symptoms and lower incidence of adverse effects (e.g. extrapyramidal symptoms) than conventional antipsychotics. In consequence of the increasing prescription accidental and

intentional poisonings by atypical antipsychotics also increased (see Figure). All sufficiently documented cases of poisoning with atypical antipsychotics reported to the Poison Information Centre (PIC) Erfurt from 1994 to 2003 were analysed retrospectively to give more information about the toxicity of atypical antipsychotics and the poisoning patterns.

2. Case Series

Number of cases:

865 cases, 343 of them were single drug ingestions (1994-2003) rose from 26 in 1994 to 187 in 2003 (corresponding to 1 and 2,7 % of the total number of calls for drug overdose in these years)

Age: 4 months – 85 years (see Table)

309 adults (90,1 %), 29 children (8,4 %), 5 of unknown age (1,5 %)

Dose: range 0,2 to 200-fold DDD (see Table)

Cause of poisoning: suicide attempts represent the main proportion of all cases (78 %), the others were accidental overdoses (approx. 17 %), cases of drug abuse or adverse effects.

Table: Single drug ingestion of atypical antipsychotics

Drug	Cases	Age (years) median (range; n)	Dose (mg/kg) median (range; n)	DDD (mg/kg)	Rate of overdosing (factor of DDD)
Amisulpride	16	24 (2 - 48; 11)	57,1 (3,6 - 343; 16)	5,71	0,6 - 60
Clozapine	74	32 (1,25 - 80; 54)	16,4 (0,71 - 257; 49)	4,29	0,2 - 60
Olanzapine	86	34 (1,25 - 80; 64)	2,1 (0,29 - 28,6; 74)	0,14	2 - 200
Quetiapine	21	29,5 (14 - 65; 18)	27,3 (13,1 - 300; 18)	5,71	2,3 - 52
Risperidone	66	22 (0,3 - 85; 49)	0,5 (0,04 - 4,3; 61)	0,07	0,5 - 60
Sulpiride	43	25 (2 - 64; 37)	28,6 (2,1 - 185; 34)	11,43	0,2 - 16
Ziprasidone	5	14 (14 - 48; 3)	17,10 (2,9 - 57; 3)	1,14	2,5 - 50
Zotepine	32	41 (2 - 63; 24)	25,0 (1,9 - 143; 26)	2,86	0,7 - 50

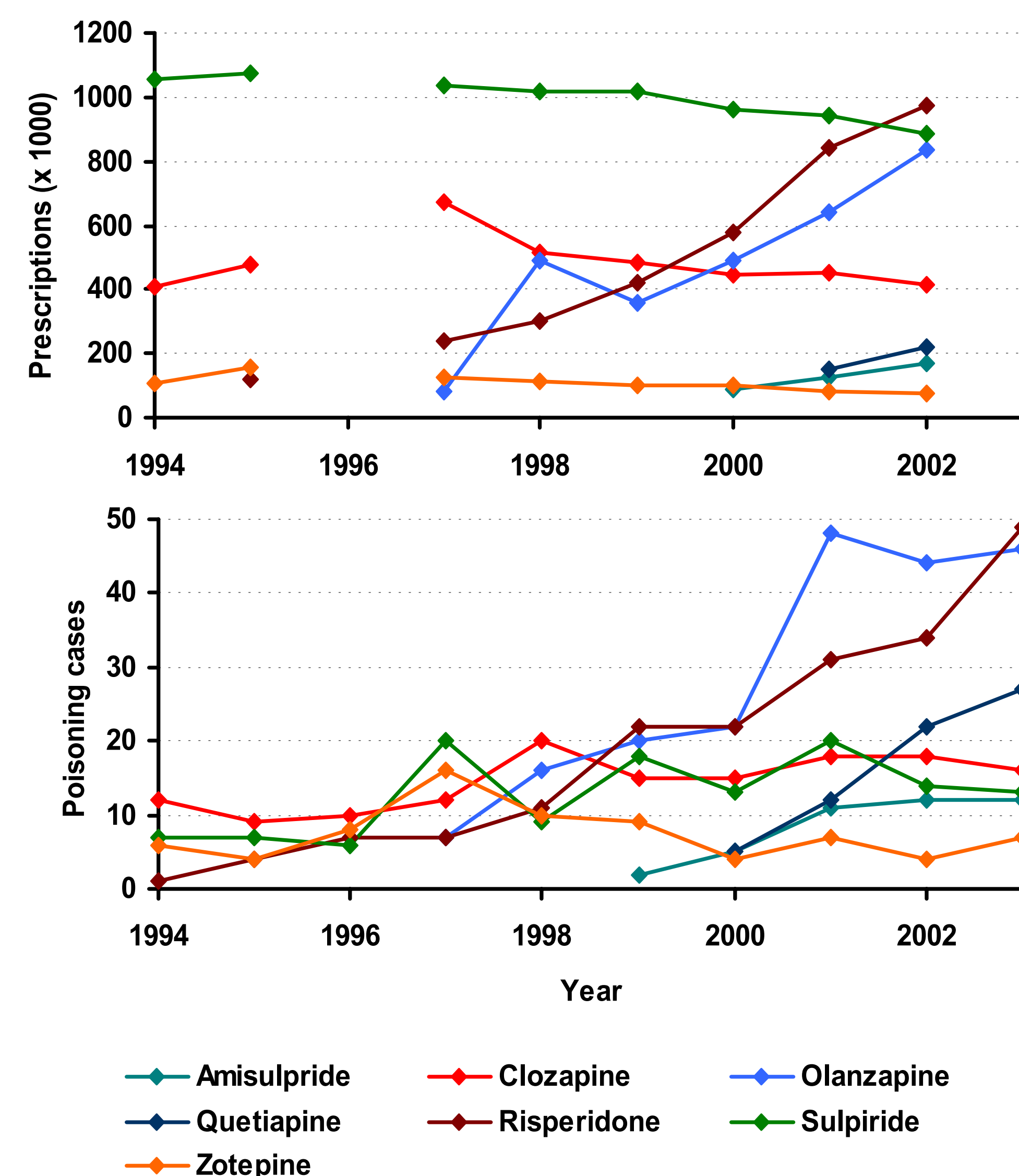


Figure: Number of prescriptions of atypical antipsychotics in Germany and poisoning cases reported to the PIC Erfurt

3. Clinical Feature of Poisoning

Clinical feature of poisoning:

- similar for all atypical antipsychotics
- predominantly characterised by CNS depression, in some cases alternating with agitation
- common clinical effects: tachycardia, hypotension, extrapyramidal effects

Range of toxicity:

- doses of two- to fivefold DDD → extrapyramidal disturbances (with amisulpride already at therapeutic doses)
- doses up to the five- to tenfold DDD → in most cases minor symptoms
- doses above the five- to tenfold DDD → loss of consciousness may be possible, however, respiratory depression and seizures occurred rarely
- one case of fatality was registered with amisulpride (343 mg/kg, e.g. 60 DDDs).

Incidence of clinical effects after single drug overdosing of atypical antipsychotics in 240 patients:

- **CNS: clouding of consciousness (somnolence – coma, 68 %), extrapyramidal effects (13,8 %), agitation (12 %)**, hallucinations (6,7 %), dizziness (3,3 %), respiratory depression (2,9 %), seizures (2,1 %), disturbances in thermoregulation (1,2 %), stupor (1,3 %), tremor (0,8 %), headache (0,8 %)
- **Cardiovascular system: tachycardia (19,6 %)**, hypotension (8,3 %), dysrhythmia (3,3 %), bradycardia (1,3 %)
- **Gastrointestinal tract: vomiting (6,2)**, nausea (1,2 %), dryness of the mouth (1,2 %), hypersalivation (2,9 %)
- **Eyes: miosis (5,4 %)**, mydriasis (2,1 %), visual disturbances (1,3 %)
- **Skeletal muscles: fasciculations/myocloni (2,1 %)**, elevation of myoglobin/creatin kinase in serum (1,3 %), myalgia (0,8 %)
- **Skin: warm and dry skin and mucosa (3,3 %)**, hyperhidrosis (1,7 %)
- **Others:** in particular cases hepatic or renal dysfunction, dysuria, leucocytosis, hypoglycaemia, hypokalaemia, hyperprolactinaemia

4. Conclusions

➤ Generally, the newer atypical antipsychotics appear to have the same overdose profile as phenothiazines and butyrophenones. Essentially, the toxic-therapeutic ratio is not much better, but acute overdose results seldom in death.

➤ Finally, clozapine seems to be more toxic than the others, since this drug caused unconsciousness, tachycardia and cardiac arrhythmias even at doses below DDD.