

Clinico-toxicological assessment of newer antidepressants

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Objective

Newer antidepressants (selective serotonin reuptake inhibitors, reboxetine, venlafaxine, mirtazapine and moclobemide) are thought to be safer in overdose than tricyclic antidepressants (1,2). In order to obtain more information about their toxicity and poisoning patterns all sufficiently documented cases with single drug ingestion of newer antidepressants reported to the Poison Information Centre Erfurt from 1995 to 2004 were analysed retrospectively.

Case Series PIC Erfurt 1995 - 2004

Number of cases:

456 single drug ingestions (29 %) of 1572 poisoning cases with newer antidepressants, increased from 25 in 1995 to 382 in 2004 (corresponding to 1.1 and 7.5 % of the total number of calls for drug overdose in these years)

Patients: age 0.2 - 88 years (see Table)

419 adults (91.9 %), 34 children (7.5 %), 3 of unknown age (0.7 %)

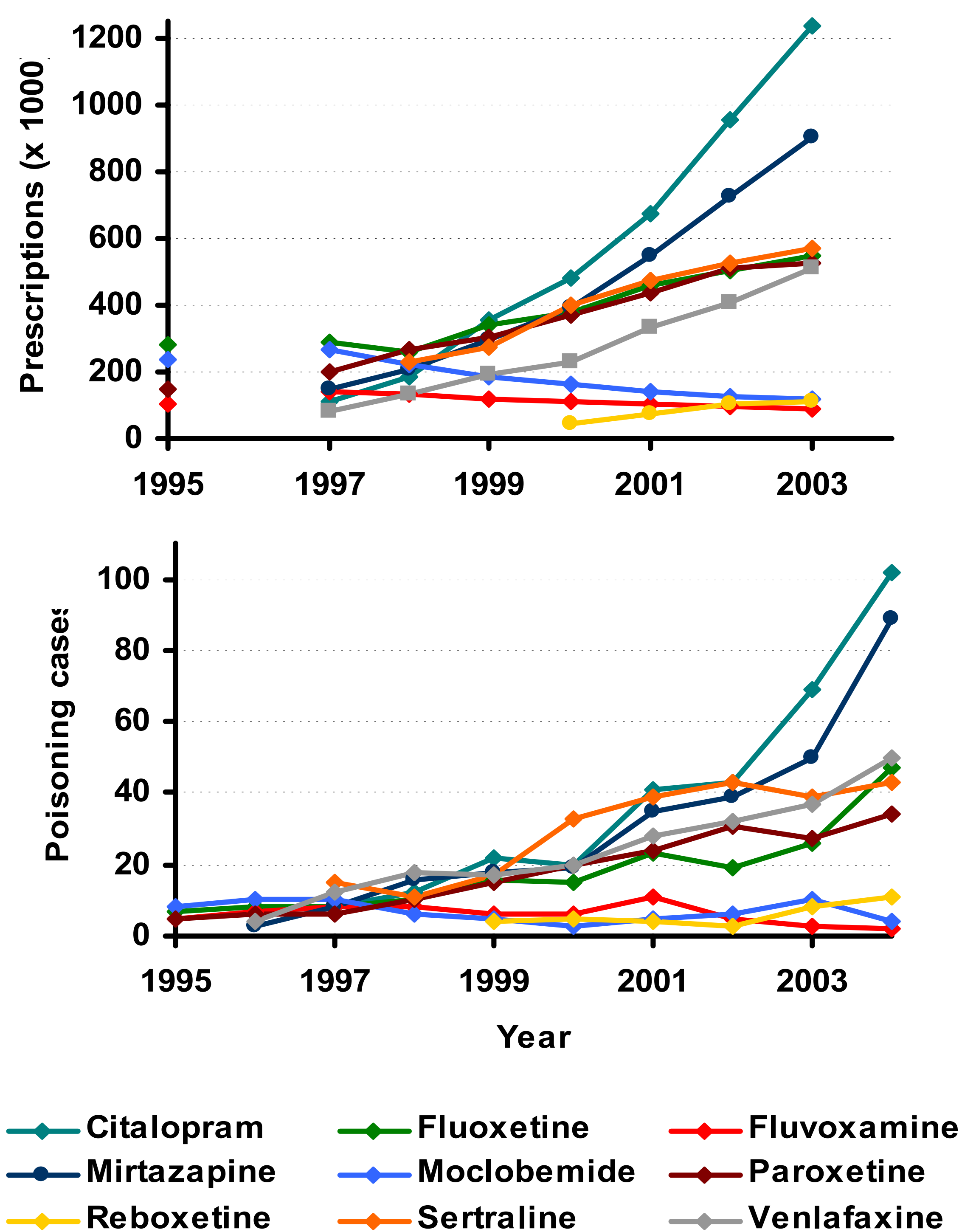
Dose: 1.5 to 600-fold DDD (see Table)

Cause of poisoning:

295 suicide attempts (65 %), 41 accidental overdoses (9 %), 6 misuses (1.3 %), 3 abuses (0.7 %), 111 unknown (24 %)

Estimated risk:

19 nontoxic (4.2 %), 209 possibly toxic (45.8 %), 99 minor toxic (21.7 %), 45 moderate toxic (9.9 %), 30 severe toxic (6.6 %), 54 unpredictable (11.8 %)



Number of prescriptions of newer antidepressants in Germany and poisoning cases reported to the PIC Erfurt

References

1. Isbister GK, Bowe SJ, Dawson A, Whyte IM (2004) Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 42: 277-285
2. Kelly CA, Dhaun N, Laing WJ, Strachan FE, Good AM, Bateman DN (2004) Comparative toxicity of citalopram and the newer antidepressants after overdose. *J Toxicol Clin Toxicol* 42: 67-71

Drug	Cases	Age (years) median (range; n)	Dose (mg/kg) median (range; n)	DDD mg/kg	Rate of overdosing (factor of DDD)
Citalopram	100	33 (2 - 79; 68)	7 (0.43 - 171; 90)	0.29	1.5 - 600
Fluoxetine	46	19 (2 - 54; 30)	5 (0.5 - 57; 42)	0.29	22 - 200
Fluvoxamine	25	30 (14 - 70; 19)	21 (7.1 - 214; 22)	0.14	5 - 150
Mirtazapine	93	40 (2 - 88; 55)	8 (1.1 - 62; 83)	0.43	2.5 - 144
Moclobemide	14	45 (2 - 61; 11)	86 (32 - 429; 9)	4.3	7.5 - 100
Paroxetine	47	20 (0.2 - 48; 33)	6 (0.57 - 129; 40)	0.29	2 - 450
Reboxetine	6	22 (1 - 55; 5)	1 (0.4 - 3.21; 6)	0.11	3.5 - 28
Sertraline	60	25 (4 - 79; 43)	14 (1.1 - 286; 57)	0.71	2 - 400
Venlafaxine	65	38 (15 - 69; 39)	24 (4.3 - 143; 62)	1.43	3 - 100

Table: Single drug ingestions of newer antidepressants

Clinical Feature of Poisoning

- gastrointestinal disturbances (26 %) and tachycardia (20 %) are common
- predominantly characterised by CNS depression (incidence 53 %) sometimes accompanied by agitation (15 %), especially in sertraline poisoning
- seizures occurred (8 %) especially after overdose of citalopram and venlafaxine
- cardiac arrhythmias are possible (2.6 %), however, two fatalities caused by cardiac arrest occurred with citalopram (4 g) and venlafaxine

Incidence of clinical signs after single drug overdosing of newer antidepressants in 268 patients:

- **CNS: clouding of consciousness (somnolence – coma, 53 %), agitation (15 %),** tremor (9 %), seizures (8 %), dizziness (4.5 %), extrapyramidal signs (4.1 %), confusion (3.4 %), respiratory depression (2.2 %), headache (1.5 %), disturbances in thermoregulation (1.5 %), anxiety (1.1 %), paracousis
- **Cardiovascular system: tachycardia (20 %),** hypotension (3.7 %), hypertension (2.6 %), dysrhythmia (2.6 %), bradycardia (1.1 %), cardiac arrest (two cases)
- **Gastrointestinal tract: nausea/vomiting (24 %),** dryness of the mouth (2.6 %), abdominal pain (1.5 %), diarrhoea (0.7 %)
- **Eyes: mydriasis (9 %),** nystagmus (0.7 %), visual disturbances (0.7 %)
- **Skeletal muscles: fasciculations/myocloni (1.5 %),** hyperreflexia or areflexia (1.1 %), myoglobinaemia and CK increase (0.7 %), muscular rigidity (0.7 %)
- **Skin: hyperhidrosis (3.4 %),** warm and dry skin and mucosa (1.1 %),
- **Others: in particular cases hepatic or renal dysfunction, dysuria, electrolyte imbalance, leucocytosis, acidosis**

Range of Toxicity

Multiple of DDD	Symptoms
> 3-5	mostly mild symptoms (fatigue, restlessness, nausea, vomiting)
> 6-15	tachycardia
> 10-20	unconsciousness
> 50-100	seizures (venlafaxine > 14)

Conclusion

- From toxicological point of view we confirm a more favourable safety of newer antidepressants in comparison to tricyclic antidepressants.
- The incidence of seizures in overdose of newer antidepressants seems to be higher with citalopram and venlafaxine, tachycardia is more frequently observed with venlafaxine.
- Fatality with more than 100-fold therapeutic dose may occur.