

Benzodiazepines and suicidal ideation and completed suicide

Introduction

The benzodiazepines available on the Dutch market are Alprazolam (Xanax[®]) [1], bromazepam [2], chlordiazepoxide [3], clobazam (Frisium[®]) [4], Clorazepate (Tranxène[®]) [5], diazepam (Stesolid[®], Diazemuls[®] and generic tablets) [6,7], lorazepam (Temesta[®], Dormonoc[®]) [8,9], oxazepam (Seresta[®]) [10], prazepam (Reepam[®]) [11], flunitrazepam [12], flurazepam (Dalmadorm[®]) [13], lormetazepam (Noctamid[®]) [14], midazolam (Dormicum[®]) [15], nitrazepam (Mogadon[®]) [16], temazepam (Normison[®]) [17] and brotizolam (Lendormin[®]) [18].

The first of these benzodiazepines which was granted marketing authorisation in the Netherlands was nitrazepam, in 1966 [16].

Benzodiazepines are indicated for *the treatment of pathological anxiety and tension* [1-5,7,8,10,11]. They are also indicated for *the (short-term) treatment of sleep disorders* [7,9,10,12-18]. Clobazam is also registered as *adjuvant therapy in patients with epileptic attacks, when the patient cannot be stabilized enough with only anti-epileptics* [4]. Diazepam is also indicated for *muscle spasms, symptoms of acute alcohol abstinence and adjuvant therapy for convulsions* [7]. Diazepam per rectiole is also registered for *the treatment of status epilepticus and fever convulsions in children* [6]. Lorazepam is also *indicated as premedication for surgery* [10] [9]. Nitrazepam is also *indicated for epilepsy; West's syndrome and Lennox's syndrome* [16].

Suicidal ideation and behavior are among the most serious and common psychiatric emergencies. Suicide is the tenth leading cause of death worldwide. Reported rates of suicide, however, may underestimate the true burden because of misclassification of death due to legal or social stigma and procedural issues related to death registration. A variety of factors are associated with an increased risk of suicide; psychiatric disorders, hopelessness and impulsivity, history of previous suicide attempts or threats, marital status, health, adverse childhood experiences, family history and genetics and the use of antidepressants. The risk of suicide increases with increasing age, however young adults attempt suicide more often than older adults. Females attempt suicide four times more frequently than males, but males are successful three times more often [19].

Reports

Benzodiazepines can be found in the Lareb database under two separate ATC-5 codes, namely ATC N05BA (Anxiolytics) and ATC N05CD (Insomnia and hypnotics). Both ATC codes were taken into account in this analysis.

In the period between 25-10-2002 and 04-02-2014, Lareb received 30 reports in total, with 16 reports of suicidal ideation, 6 reports of completed suicide and 8 reports of suicide attempt associated with the use of a benzodiazepine. The total number of benzodiazepines involved is 36. Between one (2002) and six (2010) reports were received per year.

For completed suicides, the benzodiazepines involved were alprazolam (n=3), oxazepam (n=2) and clobazam (n=1).

For suicidal ideation the benzodiazepines involved were alprazolam (n=9), oxazepam (n=4), bromazepam (n=1), lormetazepam (n=1), temazepam (n=2) and nitrazepam (n=1).

For suicide attempts the benzodiazepines involved were clobazam (n=2), oxazepam (n=3), lorazepam (n=2), nitrazepam (n=1), temazepam (n=1), diazepam (n=2). Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Of the 30 patients, 11 were male and 19 were female. The patient's age ranged from 9 to 71 years with a mean of 44.8 years (Standard Deviation 16.1 years).

Reported indications for use were stress/feeling tense (n=4), burn-out (n=1), obsessive compulsive disorder (n=1), anxiety (n=3), panic (n=1), Borderline personality disorder (n=1), emotional distress (n=1), epilepsy (n=1), insomnia/sleep disorder (n=3).

In 15 reports either an antidepressant or an antipsychotic drug was used as suspect or concomitant medication next to the use of the suspected benzodiazepine. In four reports the patient used an antiepileptic drug, namely carbamazepine, phenytoin, topiramate, levetiracetam and lacosamide. The patient who used topiramate also used acamprosate (Campral®) as concomitant medication, which is indicated in the treatment of alcoholism. The patient who used levetiracetam and lacosamide had been somber since the use of the anti-epileptic drugs, which were used for epilepsy caused by a brain tumor.

The latency of the reaction was known in 23 cases. Reported latencies varied from 1 hour to 5 years. Mean latency was 240 days, Median latency was 9 days. In 16 cases the reported latencies were hours to less than 10 days.

Two cases which were reported, were based on published literature [20,21] and reported to Lareb through the Marketing Authorization Holder (MAH).

In 6 cases the outcome was fatal. In 6 cases the use of the benzodiazepine was discontinued and the patient recovered (positive dechallenge). However, one of these patient recovered after treatment with haloperidol. In one case the benzodiazepine was withdrawn and the patient recovered after being admitted to a psychiatric hospital. Another contributing factor in this patient was borderline personality disorder. Three patients discontinued the use of the benzodiazepine but had not recovered at the time of reporting. One patient discontinued the use with an unknown outcome. In one patient there was no change in the use of the benzodiazepine and of fluoxetine, but she recovered with sequel of her suicidal tendencies after getting care from a nurse. In the other cases it is unknown what the action with the suspect drug and outcome were.

Below four index cases are described:

Patient A (91123)

This well documented serious spontaneous report from a pharmacist concerns a female aged 51-60 years, with aggravation of anxiety, suicidal tendency and amnesia following administration of alprazolam for anxiety with a latency of 3 days after start. Alprazolam was prescribed as additional treatment with fluvoxamine that was started about 1.5 year before. The drug was tapered-off in five days and the patient recovered with sequel - she still has amnesia symptoms. Concomitant medications were formoterol, losartan, fluvoxamine and ciclesonide. The patient's medical history consists of depression.

Patient B (62225)

This well documented serious spontaneous report from a consumer concerns a female aged 51-60 years, with suicidal ideation and aggressiveness following administration of bromazepam for nervous tension with a latency of 4 days after start. The patient's spouse described this as near-psychotic symptoms. The patient was admitted in a psychiatric hospital. Bromazepam was withdrawn. The patient recovered. Concomitant medication was not reported.

Patient C (54132)

This well documented serious spontaneous report from a consumer concerns a female aged 31-40 years, with agitation, self-mutilation, suicidal ideation and aggressive reaction following administration of alprazolam for a panic reaction with

a latency of 5 days after start. The patient recovered. Concomitant medications were oxazepam, venlafaxine, levomepromazine and olanzapine. All concomitant medication, except for olanzapine had been used for years. Olanzapine was started on the same date as alprazolam. However, this drug was discontinued two weeks earlier and the patient only recovered after alprazolam was discontinued. Stress was mentioned as an additional factor.

Patient D (115722)

This well documented serious spontaneous report from a consumer concerns a male aged 70 years and older, with psychosis, aphasia and suicide attempt following administration of lorazepam for a sleep disorder with a latency of 5 hours after start. The drug lorazepam was withdrawn after three days. The patient was treated with haloperidol. The patient recovered. Concomitant medications were a non-specified antibiotic and prednisolone, both started three days earlier for an unknown indication. Both concomitant medications were withdrawn two weeks after lorazepam was withdrawn. Earlier use of lorazepam by this patient led to the occurrence of dream anxiety.

Other sources of information

SmPC

In section 4.4. of the SmPC (Special warnings and precautions for use) of almost all benzodiazepines available in the Netherlands it is described that benzodiazepines should not be used as monotherapy for the treatment of depression or anxiety related to depression because this could lead to suicide/suicidal ideation [1-4,6,8,9,11,13-18].

Some SmPC's also describe in section 4.8 (Adverse Drug Reactions) that pre-existing depression can manifest itself during the use of benzodiazepines or mention depression [3,6-9,9-11,15-18].

The SmPC of clobazam explicitly mentions suicidal ideation under section 4.8 [9]. The SmPC of lorazepam mentions completed suicide and suicidal ideation as a manifestation of pre-existing depression [14].

Literature

A study looking at risk of suicide attempts after benzodiazepine and/or antidepressant use included a population of 225,796 persons with prescriptions for benzodiazepines from the Saskatchewan Health Data Bases. Controls consisted of 97,862 individuals who did not receive benzodiazepines. The results of this study show that using a benzodiazepine and/or an antidepressant is associated with substantially increased rates of hospital admission for suicides when compared to unexposed controls.

Stratifying the populations into antidepressant users and non-antidepressant users indicated that non-antidepressant users had statistically significant associations between suicide attempts and benzodiazepine use (odds ratio (OR) = 6.2). This study concluded that the association between benzodiazepine use and attempted suicide is especially high for non-antidepressant users, for the young, and for males. Whether this relationship is causal or not, physicians should be aware of the high potential for suicide attempts when prescribing benzodiazepines for patients in these high risk groups [22].

A review by Youssef and Rich [23] concluded that is considerable evidence that sedative/hypnotics produce depressant and/or disinhibitory effects in a small proportion (perhaps 5%) of people who take them. However, there is no clear evidence that their brief use early in depression increases suicide risk. Toxicological data of suicides indicate that a majority of people who commit suicide

are under the influence of sedative/hypnotic chemicals (including alcohol) at the time.

Databases

On January 30th 2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained 30 reports of suicidal ideation, attempted suicide or completed suicide associated with the use of benzodiazepines. Because one report can contain multiple suspect drugs, the total number of benzodiazepines associated with suicidal behaviour is 36. All reporting odds ratios were disproportional (see table 1).

Table 1. Reports of Suicidal and self-injurious behaviour for the benzodiazepines in the Lareb database

HLT-term	Drug	Number of reports	ROR (95% CI)
Suicidal and self-injurious behaviour	Temazepam	4	4.8 (1.8 – 12.9)
	Lormetazepam	1	-
	Alprazolam	11	21.3 (11.3 – 40.1)
	Oxazepam	8	8.1 (4.0 – 16.5)
	Clobazam	3	10.3 (3.2 – 33.3)
	Bromazepam	1	-
	Lorazepam	4	9.1 (3.3 – 25.0)
	Diazepam	2	-
	Nitrazepam	2	-
	Total	36	8.8 (6.3 – 12.4)

The WHO database of the Uppsala Monitoring Centre contained 11042 reports of MedDRA® Preferred Term (PT) Completed suicide, Suicide attempt and Suicidal ideation falling under High Level Term (HLT) Suicidal and self-injurious behaviour associated with the use of benzodiazepines. These associations are almost all disproportionally reported. See Table 2.

Table 2. Reports of completed suicide, suicide attempt and suicidal ideation for the benzodiazepines in the WHO and Eudravigilance database.

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)
WHO	Completed suicide	Alprazolam	2256	47.5 (45.4-49.7)
		Clonazepam	1214	37.5 (35.3-39.9)
		Oxazepam	46	4.7 (3.5-6.2)
		Lorazepam	786	18.7 (17.4-20.1)
		Diazepam	1138	25.9 (24.1-27.5)
		Chlordiazepoxide	89	20.6 (16.1-24.8)
		Nordazepam	22	16.1 (24.9-38.3)
		Bromazepam	26	2.4 (1.6-3.5)
		Temazepam	342	33.7 (30.1-37.7)
		Flurazepam	66	15.5 (12.1-19.8)
		Nitrazepam	6	1.3 (0.6-2.8)
		Lormetazepam	5	1.7 (0.7-4.1)
		Flunitrazepam	9	1.2 (0.6-2.4)
		Total	5605	33.5 (32.5-34.5)

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)	
	Suicide Attempt	Alprazolam	587	9.7 (8.9-10.6)	
		Clonazepam	327	3.4 (2.5-4.3)	
		Oxazepam	320	33.1 (29.4-38.7)	
		Lorazepam	1180	27.0 (25.4-28.7)	
		Diazepam	443	8.7 (7.9-9.5)	
		Chlordiazepoxide	101	21.2 (17.3-25.9)	
		Bromazepam	179	15.8 (13.6-18.4)	
		Prazepam	15	5.6 (3.4-9.3)	
		Clobazam	30	4.8 (3.3-6.9)	
		Temazepam	131	11.1 (9.4-13.3)	
		Flurazepam	93	20.6 (16.7-25.4)	
		Nitrazepam	140	29.6 (24.9-35.2)	
		Lormetazepam	58	19.5 (15.0-25.5)	
		Flunitrazepam	75	9.8 (7.8-12.4)	
		Total	3679	15.8 (15.3-16.4)	
	Suicidal ideation	Alprazolam	254	3.7 (3.3-4.2)	
		Clonazepam	204	4.7 (4.1-5.4)	
		Oxazepam	0	-	
		Lorazepam	146	2.7 (2.3-3.2)	
		Diazepam	110	1.9 (1.6-2.3)	
		Chlordiazepoxide	0	-	
		Bromazepam	0	-	
		Prazepam	0	-	
		Clobazam	0	-	
		Temazepam	27	2.0 (1.4-3.0)	
		Flurazepam	12	2.3 (1.3-4.0)	
		Nitrazepam	5	0.9 (0.4-2.1)	
		Lormetazepam	0	-	
		Flunitrazepam	0	-	
		Total	758	2.6 (2.4-2.8)	
	Total		11042	17.2 (16.8-17.5)	
	Eudravigilance	Completed suicide	Alprazolam	1443	29.0 (27.4 – 30.7)
			Clonazepam	1015	21.6 (20.2 – 23.1)
			Oxazepam	44	3.5 (2.6 – 4.7)
			Lorazepam	602	12.2 (11.2 – 13.3)
			Diazepam	886	17.6 (16.4 – 18.8)
Chlordiazepoxide			82	49.4 (38.5 – 63.4)	
Nordazepam			14	8.0 (4.7 – 13.6)	
Bromazepam			41	1.9 (1.4 – 2.6)	
Temazepam			241	34.5 (30.0 – 39.7)	
Flurazepam			40	15.4 (11.1 – 21.3)	
Nitrazepam			13	2.6 (1.5 – 4.6)	
Lormetazepam			11	2.5 (1.4 – 4.6)	
Flunitrazepam			43	3.0 (2.2 – 4.0)	
Total			4475	20.0 (19.3 – 20.7)	
Suicide Attempt			Alprazolam	381	6.4 (5.8 – 7.1)
		Clonazepam	399	7.6 (6.9 – 8.5)	

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)
		Oxazepam	206	18.1 (15.7 – 21.0)
		Lorazepam	1136	25.4 (23.9 – 27.1)
		Diazepam	419	7.7 (7.0 – 8.5)
		Chlordiazepoxide	7	3.2 (1.5 – 6.9)
		Bromazepam	270	13.5 (11.9 – 15.3)
		Prazepam	24	8.5 (5.7 – 12.9)
		Clobazam	31	3.4 (2.4 – 4.8)
		Temazepam	85	10.6 (8.5 – 13.2)
		Flurazepam	72	30.2 (23.4 – 38.9)
		Nitrazepam	163	41.8 (35.1 – 49.7)
		Lormetazepam	54	13.3 (10.1 – 17.6)
		Flunitrazepam	169	12.5 (10.7 – 14.7)
		Total	3416	13.6 (13.1 – 14.1)
	Suicidal ideation	Alprazolam	146	2.5 (2.2 – 3.0)
		Clonazepam	182	3.6 (3.1 – 4.2)
		Oxazepam	25	2.1 (1.4 – 3.1)
		Lorazepam	101	2.0 (1.7 – 2.4)
		Diazepam	109	2.0 (1.7 – 2.5)
		Chlordiazepoxide	2	1.0 (0.2 – 3.9)
		Bromazepam	23	1.1 (0.7 – 1.7)
		Prazepam	0	-
		Clobazam	13	1.5 (0.9 – 2.6)
		Temazepam	22	2.8 (1.8 – 4.2)
		Flurazepam	9	3.4 (1.8 – 6.6)
		Nitrazepam	7	1.5 (0.7 – 3.2)
		Lormetazepam	4	1.0 (0.4 – 2.6)
		Flunitrazepam	9	0.7 (0.3 – 1.3)
		Total	652	2.3 (2.1 – 2.5)
	Total		8543	15.0 (14.6 – 15.4)

Prescription data

Table 3. Number of patients using benzodiazepines in the Netherlands between 2008 and 2012 [24].

Drug	2008	2009	2010	2011	2012
ATC-code N05BA					
Diazepam	376,210	69,034	76,293	78,907	75,242
<u>Chloordiazepoxide</u>	14,252	5,300	5,111	5,185	4,388
<u>Oxazepam</u>	626,430	108,930	121,310	130,570	132,740
<u>Clorazepate</u>	25,719	9,805	10,297	10,263	10,162
<u>Lorazepam</u>	73,526	27,719	31,967	35,231	37,930
<u>Bromazepam</u>	35,191	7,218	7,498	7,579	7,474
<u>Clobazam</u>	11,689	7,726	7,859	8,069	8,231
<u>Prazepam</u>	3,872	989	913	855	806
<u>Alprazolam</u>	79,297	23,351	25,706	27,978	28,051

ATC code N05CD

Drug	2008	2009	2010	2011	2012
<u>Flurazepam</u>	20,098	7,523	7,623	7,263	6,833
<u>Nitrazepam</u>	62,222	10,378	10,153	9,950	9,567
<u>Flunitrazepam</u>	6,944	2,179	2,183	2,042	1,980
<u>Lormetazepam</u>	70,240	16,486	17,095	17,398	17,116
<u>Temazepam</u>	498,840	78,829	85,350	91,682	92,384
<u>Midazolam</u>	43,746	20,620	22,924	25,877	27,807
<u>Brotizolam</u>	7,031	1,174	1,121	1,160	1,159
<u>Loprazolam</u>	8,937	1,267	1,301	1,335	1,311

Mechanism

Benzodiazepines may cause disinhibition, consisting of poor impulse control and paradoxical reactions that may induce suicidal impulse. The release of aggression in susceptible patients may be directed towards others but could, especially in depressed patients, be directed towards themselves. However, it could also be that treatment with benzodiazepines may be inappropriate for patients with an underlying depression as they are central nervous system depressants and may worsen an underlying depression. Approximately 50% of suicides have a history of major depression and pre-existing depression is considered a major factor in suicides [22].

Discussion and conclusion

Lareb received 30 reports of suicidal ideation, suicide attempts and completed suicides associated with the use of benzodiazepines. In many cases the patient's used an antidepressant drug as concomitant medication or as another suspect drug. Depression was not mentioned as an indication for use of the benzodiazepines. Indications most often reported for the benzodiazepines were stress, anxiety and sleep disorders. Reported indications for use like Borderline personality disorder may lead to a higher risk of suicidal behavior in patients [25] and the use of suspect/concomitant medication like anti-epileptic drugs has also been associated with suicidal behavior [26].

Latencies varied from 1 hour to years, but in 16 cases the reported latencies were hours to 9 days. The association of benzodiazepines with suicidal ideation or behaviour is supported by a statistically significant disproportionality in the database of Lareb and the WHO. In section 4.4. of almost all SmPC's of benzodiazepines available on the Dutch market there is a warning that benzodiazepines should not be used as monotherapy for the treatment of depression or anxiety related to depression because this could lead to suicide/suicidal ideation [1-4,6,8,9,11,13-18]. Some SmPC's also describe in section 4.8 (Adverse Drug Reactions) that pre-existing depression can manifest itself during the use of benzodiazepines or mention depression [3,6-9,9-11,15-18]. Considering the serious and potentially life-threatening nature of this ADR, suicidal ideation and –behavior should be mentioned in section 4.8 of all benzodiazepines.

- Suicidal ideation and/or suicidal behavior should be mentioned in the SmPC of all benzodiazepines

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