Phenazepam

Pre-Review Report

Agenda item 5.8

Expert Committee on Drug Dependence

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Contents

Acknowledgements

Summary

Phenazepam belongs to the 1,4-benzodiazepines, the same family of medicines to which diazepam, oxazepam and temazepam belong. Phenazepam was first synthesized and developed in 1975 in the former Soviet Union where it became one of the most prescribed benzodiazepines since 1978 to treat sleep disorder, anxiety, alcohol use disorder and epilepsy. Phenazepam has not been licensed elsewhere in the world. The limited licensed use explains the scarcity of peer-reviewed literature about phenazepam not written in Russian.

The pharmacological profile of phenazepam fits well that of the classical benzodiazepines. Phenazepam diminishes anxiety, convulsions and locomotor activity. It is more potent than diazepam (about a factor of 5 to 10), and has more severe and longer lasting adverse effects. The actions of phenazepam are mediated by the $GABA_A$-receptor and reversed by the selective benzodiazepine antagonist flumazenil. In humans, phenazepam has a relatively long elimination half-life of 60 hours and adverse effects may last for up to 5 days (some reports mention up to 3 weeks) after ingestion.

In vitro, phenazepam and its metabolite 3-hydroxyphenazepam potentiate GABA responses with EC_{50}-values of 6.1 nM and 10.3 nM, respectively, comparable to the value of 13.5 nM for diazepam. *In vivo*, phenazepam induces pronounced myorelaxation in the rotarod test with an ED_{50}-value of 2.48 (1.65-3.72) mg/kg, and at 10 mg/kg it decreases punished responding in the conflict test (conflict between drinking motivation and painful electrical stimuli). Phenazepam increases the duration of sleep induced by hexanal several fold and is in this respect superior to diazepam. Convulsions induced by high doses of metrazol (100 mg/kg) are completely prevented by phenazepam (1.4 mg/kg). In a double-blind clinical study, phenazepam (0.0025 mg/kg) showed a more pronounced and longer lasting sedation than diazepam (0.005 mg/kg).

At a relatively high dose, phenazepam induces muscle hypotonia, deep sleep, and coma. Like other benzodiazepines, phenazepam has severe toxicity when concomitantly used with other CNS depressant drugs, especially opioids and alcohol, which increases the risk of respiratory depression and death. Various fatal cases have been described following ingestion of phenazepam (analytically confirmed), mostly in combination with other CNS depressant drugs.
Abuse of phenazepam has been reported. Following relatively high dosages or long-term use of phenazepam, signs of withdrawal are seen. Although withdrawal following phenazepam has been reported in human, explicit studies on the dependence potential in humans have not been described, but presumably fall – due to its high potency and duration of action - in the higher range of the conventional benzodiazepines. Phenazepam has regularly been found in samples seized by police or customs.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable

B. *Chemical Abstract Service (CAS) Registry Number*

51753-57-2

C. *Other Names*

fenazepam
7-bromo-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one
7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-one

D. *Trade Names*

BD 98, Elzepam, Phenazepam, Phezipam, Phenorelaxan, Fenazepam, Phenzitat

E. *Street Names*

Bonsai, Bonsai Supersleep, Fenaz, Soviet Benzo

F. *Physical properties*

Pure phenazepam is a white crystalline powder with a greyish-yellow tinge, odourless and tasteless, insoluble in water and soluble in ethanol (~0.2 mg/ml), dimethylformamide and chloroform (20 mg/ml). The log P-value is 4.29.

G. *WHO Review History*

Phenazepam has not been previously reviewed by the Expert Committee on Drug Dependence of the WHO.

2. Chemistry

A. *Chemical Name*

IUPAC Name:
7-bromo-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one

CA Index Name:
Not applicable

B. *Chemical Structure*

Free base:
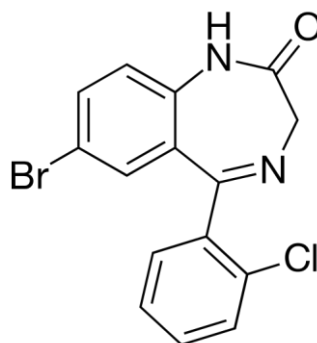
Molecular Formula:	$C_{15}H_{10}BrClN_2O$
Molecular Weight:	349.6
Melting point:	225-230 ºC
Boiling point:	not reported

C.   *Stereoisomers*

No stereoisomers possible

D.   *Synthesis*

Methods of manufacturing:
The synthesis of phenazepam has been described by Sozinov *et al.*[1]

E.   *Chemical description*

Phenazepam is a heterocyclic compound with a diazepine ring fused to a phenyl ring. It has strong structural resemblance to the classical benzodiazepine diazepam.

F.   *Chemical properties*

Phenazepam is a weak base. Its pK_a-value has not been described.

G.   *Chemical identification*

Spectral data: UV spectrum λ_{max} 229, 322 nm; IR spectrum 1700 cm^{-1}.[2]
Tablets containing phenazepam were analysed by mass spectrometry and a typical isotopic pattern was observed characteristic of a compound which has one bromine and one chlorine atom at m/z 349, 351, and 353.[3]

Phenazepam can be quantified in oral fluid and post-mortem blood and urine by gas chromatography (GC) and electron capture detection[4-6], by liquid chromatography (LC)-tandem mass spectrometry (LC-MS-MS),[7-10] by GC/negative-ion chemical ionization mass spectrometry (GC/NICI-MS),[11] and by immunoassay (Syva ETSplus).[5,12] Phenazepam and its metabolite 3-hydroxyphenazepam can be quantified by LC-MS/MS in a variety of post-mortem fluids (subclavian blood, femoral blood, cardiac blood, urine, vitreous humour) and tissues (thalamus, liver).[13] Phenazepam in human hair samples has been quantified by LC-MS/MS.[14] Only a limited number of quantitation methods have been published for the

metabolites of phenazepam. 5-bromo-(2-chlorophenyl)-2-aminobenzophenone (ABPH) also known as 2-amino-5-bromo-2-chlorophenyl-benzophenone (ABCB) can be identified by thin-layer chromatography and quantitated by GC with flame ionization detection. 3-Hydroxyphenazepam can be quantitated by GC-MS (limit of detection: 1 mg/L).[15,16] With minor modifications, these methods can also be used for the chemical identification of phenazepam in pharmaceutical preparations.

3. Ease of convertibility into controlled substances

Based on its chemical structure, it is not likely that phenazepam can easily be converted into another benzodiazepine or another controlled substance.

4. General pharmacology

A. *Pharmacodynamics*

Phenazepam belongs to the group of the benzodiazepines, well-known and well-described medicinal drugs, mainly used as sedatives and anxiolytics. Phenazepam has a structure similar to that of clonazepam and properties similar to those of lorazepam in terms of therapeutic action. From a pharmacokinetic point of view, phenazepam with its long half-life is more alike clonazepam and diazepam.[17-19] Phenazepam and its metabolite 3-hydroxyphenazepam appear to be pharmacologically active with some 5- to 10-fold higher potency than diazepam, probably due to the bromine atom in the molecule. Typically, as described in older Russian literature, phenazepam is used to treat neurotic disorders, alcohol abuse disorder, epilepsy, sleep disorder, anxiety disorder, and in combination with haloperidol to treat schizophrenia. Probably, haloperidol has currently been replaced by the antipsychotic drugs olanzapine and clozapine.

Animal studies in vitro
Both phenazepam and 3-hydroxyphenazepam are full $GABA_A$ receptor agonists.[20,21] *In vitro* studies with rat cerebellar slices have shown that both phenazepam and its metabolite 3-hydroxyphenazepam potentiated GABA responses with EC_{50}'s of 6.1 nM and 10.3 nM, respectively (cf. EC_{50} of diazepam: 13.5 nM).[21,22] The potentiation of GABA responses was also shown for the metabolite 5-bromo-(2-chlorophenyl)-2-aminobenzophenone (ABPH) in isolated rat Purkinje neurones.[22,23] In experiments *in vitro*, ABPH and another metabolite of phenazepam, 6-bromo-(2-chlorophenyl) quinazoline-2-one (QNZ), also showed pharmacological activity. QNZ and ABPH exhibited biphasic effects at the $GABA_A$ receptor, initially potentiating GABA responses (that is $GABA_A$ receptor-mediated chloride currents) at low concentrations and then inhibiting them at higher micromolar concentrations.[20-23] Nitric monoxide (NO) may cause neuronal damage in cooperation with other reactive oxygen species. Pre-treatment of rats with phenazepam (2 mg/kg i.p.) significantly reduced, but did not abolish the enhancement of nitric monoxide generation evoked by pentylenetetrazole (PTZ), and dramatically decreased the elevation of thiobarbituric acid reactive substances (TBARS; biomarker of the formation of reactive oxygen species) content in cerebral cortex to control levels, suggesting a neuroprotective effect of phenazepam.[24]

Phenazepam (1 mg/kg) inhibited Ө-activity in the EEG, which is typical for benzodiazepines. Phenazepam not only inhibited the Ө-band, but also enhanced slow delta activity and high frequency β-activity.[16,25]

The reversal of withdrawal behaviour by valproate (a GABA-agonist) and alpha-methyldopa (cf. Section Dependence potential) point to a role for GABA-ergic and dopaminergic mechanisms in the action of phenazepam.[26]

Animal studies in-vivo
Studies in the albino rat showed that phenazepam, like other benzodiazepine sedatives, induced an increase in the motor activity in small doses (0.05 mg/kg), but when the dose was increased (0.5-1 mg/kg) the activating effect gradually fell, and changed into lower motor activity. Like medazepam and flunitrazepam, phenazepam at 10 mg/kg produced myorelaxation in the rat rotarod test with ED_{50}-values of 2.48 (1.65-3.72) mg/kg for phenazepam, 2.8 (1.65-3.95) mg/kg for flunitrazepam and 16.7 (9.27-30.06) mg/kg for medazepam.[27,28] At 1 mg/kg orally, phenazepam still produced myorelaxation in rotarod test: 60% of animals fell in the rotarod test and fall latency was 56.8±12.7 sec, while no falls were observed in the control group.

Phenazepam at a dose of 10 mg/kg also significantly suppressed locomotor activity and increased punished responding in the conflict test (conflict between drinking motivation and painful electrical stimuli).[27,28]

At 10-15 min after administration of phenazepam (2 mg/kg p.o.) to mini-pigs, animals were generally sedated and motor coordination was disturbed.[8] Sleep was induced at 20-40 min and was deepest at 1-2 hours after administration of phenazepam (2 mg/kg p.o.).[6] Phenazepam, in mice, increased the duration of sleep induced by hexanal several fold and was in this respect superior to nitrazepam, lorazepam, diazepam and oxazepam.[29]

In Wistar rats, phenazepam suppressed the epileptic foci and their complexes in a dose-dependent manner. At a dose of 1.4, 2.8 and 14 mg/kg i.p. or i.v., the power of the epileptic complex decreased 2.5, 2.9, and 4.8 times, respectively, at its peak compared with that in untreated animals, but the duration of the effect was not dose-dependent.[30] Convulsions induced by high doses of metrazol (100 mg/kg) that caused death in 100% of the animals, were completely prevented by phenazepam (1.4 mg/kg). In doses of 0.1-0.2 mg/kg (i.p.), phenazepam prevented death of the animals and weakened the convulsions.[31] At dose of 1.5–2 mg/kg (i.p.) phenazepam blocked pentetrazole-induced seizures.[31] Furthermore, phenazepam (2 mg/kg i.p.) was effective in reducing clonic and tonic phase of seizure attacks.[24,32] ED_{50}-values reported for inhibition by phenazepam of bicuculine- and picrotoxin-induced seizures was 0.5 mg/kg and 0.6 mg/kg i.p., respectively.[33] In blocking pentetrazole-induced seizures phenazepam was most effective at doses 1.5–2 mg/kg.[31] Pretreatment of phenazepam (2 mg/kg i.p.) 60 min prior to pentetrazole affected more the tonic seizures (33%) than the clonic seizures (78%).[24]

The selective benzodiazepine antagonist flumazenil (15 mg/kg i.p.) given 20 min before the behavioural test, completely antagonized the phenazepam-discriminative cues (at 2 mg/kg); that is following flumazenil none of the phenazepam-trained rats selected the phenazepam-appropriate lever (drug lever responses decreased from 87.2 to 3.8. These results suggest that

the discriminative effects of phenazepam were mainly mediated via the benzodiazepine binding site of the GABA$_A$–benzodiazepine receptor.[34] Like other agonists of the GABA$_A$–benzodiazepine receptor chloride channel complex, phenazepam failed to show cross-substitution of the non-benzodiazepine anxiolytic drug buspirone.[35] Furthermore, phenazepam is comparable to other benzodiazepine agonists in drug-discrimination studies with barbiturates. Like diazepam, chlordiazepoxide and midazolam, phenazepam substituted for at least 80% drug-appropriate responding in pentobarbital-trained rats.[34] Flumazenil (4 µM) inhibited the phenazepam-induced (2 µM) inhibition of evoked activity of hippocampal neurons.[36]

Human studies

Clinical studies of phenazepam, conducted in thousands of patients suffering from various neurotic, neuropathic and psychopathic disorders, accompanied by tremors, irritability, tension, anxiety, and sleep disturbance showed that phenazepam is an effective and safe sedative. Phenazepam has shown efficacy in the treatment of chronic alcoholism, especially during alcohol abstinence. It is used with success in anaesthesiology during the preparation of patients for surgical operations and is able to potentiate the action of general anaesthetics and narcotic analgesics.[29]

In a clinical trial, the effect of phenazepam was studied in patients (n=90 from three psychiatric centres in Moscow and St. Petersburg) suffering from adjustment disorder.[37] Adjustment disorder is defined as "a state of subjective distress and emotional disturbance, usually affecting the performance of social functions and performance, arising in the period of adaptation to a serious change in life or a stressful event in the life of the patient" (ICD-10 code F43.2). The study compared 46 patients treated with phenazepam with 44 patients treated with the non-benzodiazepine anxiolytic etifoxine. No difference in anti-anxiety effect based on the Hamilton Anxiety Rating Scale (Hamilton-A) was observed between both treatments. During the study, 60% of phenazepam treated patients reported "very much improved" or "much improved", while the remaining patients reported "minimal improvement." More than 75% of patients treated with etifoxine rated their condition as "very much improved" or "much improved", 10% as "minimal improvement" and 10% as "deteriorating". Eight patients in the phenazepam group dropped out of the study because of adverse effects. Reported adverse effects were drowsiness, dizziness, somnolence, difficulty in waking up (18 % of patients), muscle weakness, headache, weakening of attention, and myasthenia gravis. The results of the study suggest that phenazepam is effective in the treatment of adjustment disorders.[37]

The effect of Sydnocarb (trivial name mesocarb, a psychomotor stimulant structurally similar to the monoamine reuptake inhibitor d-amphetamine) on the myorelaxant, hypnotic, and sedative effects of phenazepam was determined in a comparative clinical trial carried out in 102 patients with anxious-depressive states. The patients received phenazepam both in combination with Sydnocarb and alone. The experiments and the clinical trials showed that Sydnocarb reduced the myorelaxant and hypnotic effects of phenazepam without influencing its sedative action. The ratio of phenazepam to Sydnocarb optimal for correcting the adverse effects of phenazepam was found to range from 1:1.25 to 1:2.5.[38]

The efficacy of phenazepam as pre-medication in anaesthesia procedures has been compared to diazepam in a double-blind study in 32 patients. Patients received oral doses of 0.0025

mg/kg and 0.005 mg/kg, respectively, 1 to 2 days before general anaesthesia. Anxiety assessed by a clinical test according to Gologorsky's scale and using the brain evoked-potential test was reduced 2 hours following oral administration of both phenazepam (0.0025 mg/kg) and diazepam (0.005 mg/kg).[39] Phenazepam elicited a more pronounced and longer lasting sedative effect as compared to diazepam. Phenazepam appeared to be a powerful anxiolytic and sedative agent and was recommended as pre-medication before surgery.[39]

B.   *Routes of administration and dosage*

In countries where phenazepam is clinically used, phenazepam is available as 0.5-mg and 1-mg tablets[40], injectable solutions (0.1%, 0.3%) and transdermal patches (Phenopercuten).[41] The clinically applied daily dose of phenazepam should not exceed 10 mg. The usual therapeutic oral dosage is 0.5 mg two to three times per day, but doses up to 10 mg/day have been reported.[42]

C.   *Pharmacokinetics*

The kinetics of phenazepam differs largely among species (rat, cat, man). For instance, the elimination half-life in rat and man is 7.5 hours and 60 hours, respectively.[16]

Animals
In mini pigs, phenazepam is rapidly adsorbed from the gastrointestinal tract. It appears in blood 30 min after administration, and reaches a maximum concentration after 2 hours.[6] A single labelled intraperitoneal dose of phenazepam administered to rats was predominantly (77%) eliminated in urine (34%) and faeces (43%) over a 5-day period.[43] The distribution volume in dogs is 2.3 to 5.6 L/kg (mean value 3.4).[44]

Humans
There is limited information available on the pharmacokinetics and metabolism of phenazepam in humans. Whereas C_{max} is attained in the rat at 1 hour, it takes in humans about 4 hours to reach a maximal value.[16] The usual clinical dose of 0.5–2.0 mg yields therapeutic concentrations in blood plasma of 20 to 60 µg/L.[45] Two healthy volunteers given a high oral dose of 3 or 5 mg phenazepam, attained peak concentrations of 24 and 38 µg/L, respectively whereas levels of 3-hydroxyphenazepam, if detectable during the time course, were lower than 3 µg/L.[16]

Phenazepam is slowly eliminated with a $T_{1/2}$ of about 60 hours which is typical for long-acting benzodiazepines[16]. However, much lower $T_{1/2}$-values of 14.9 to 15.6 hours have been reported in epileptic patients given 2 mg phenazepam intramuscularly or intravenously (cf. ref[12]. These studies suggest that the $T_{1/2}$ could be between 15 and 60 hours in man. In the study with epileptic patients receiving repeated injections of 1 mg phenazepam, the steady state plasma concentration was 157 µg/L and the estimated bioavailability was 80%.[16]

Human studies have shown that the volume of distribution (V_d) of phenazepam is 4.7-6.0 L/kg.[16] Other benzodiazepines (diazepam 0.7-2.6 L/kg; temazepam 0.8-1.0 L/ kg; and oxazepam 0.7-1.6 L/kg) have higher V_d-values, implying that phenazepam has a relatively high lipophilicity and thus sequesters more into total body fat.

Metabolism

The metabolism of phenazepam follows similar routes as of other benzodiazepines. However, limited information is available about the relative amounts of the various metabolites of phenazepam in humans. The main metabolic route of phenazepam in rodents and humans is aromatic hydroxylation.[16,42,46]

In a study in which a 5-mg oral dose of phenazepam was given to healthy volunteers, 3-hydroxyphenazepam was detected in urine samples but not in blood samples.[16] Glucuronides of hydroxylated metabolites have been found in rat and man.[20,47] Other metabolites are 5-bromo-(2-chlorophenyl)-2-aminobenzophenone (ABPH), also known as 2-amino-5-bromo-2-chlorophenylbenzophenone (ABCB),[2,22,40] and 6-bromo-(2-chlorophenyl) quinazoline-2-one (QNZ). ABPH has been detected in blood, urine, liver and kidney post-mortem samples of a suspected fatality due to phenazepam.[40] Finally, QNZ and ABPH are only likely to have significant *in vivo* pharmacological effects in overdose situations.[20,21,23] According to Drummer (2011), it is likely that, based on information from other benzodiazepines, the hydroxylation of phenazepam is catalysed by the cytochrome P450 family, specifically CYP3A.[48]
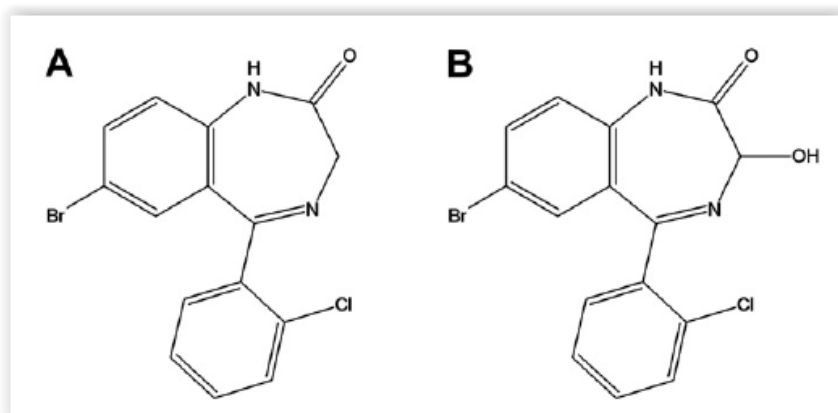
Chemical structure of phenazepam (A) and 3-OH-phenazepam (B)

Table 1. Summary of the pharmacokinetics of phenazepam in humans[42]

Parameter	Value	Dose/route	Ref.
Distribution volume	4.7-6.0 L/kg	3 or 5 mg (oral)/	
		2 mg (i.v. or i.m.)	16,49
Half-life	~ 15-60 h	3 or 5 mg (oral)	
		2 mg (i.v. or i.m.)	16,49
Bioavailability	80%	2 mg (i.v. or i.m.)	16
C_{max}	200-400 mg/L	3 or 5 mg (oral)	16
T_{max}	~ 4 h	3 or 5 mg (oral)	16
Elimination rate constant	0.044-0.047	2 mg (i.v. or i.m.)	49
Plasma clearance	220.4-267.9 ml/h	2 mg (i.v. or i.m.)	49
Steady state concentration	157.2 mg/L	Repeated 1 mg i.v.	49

5. Toxicology

The toxicity of phenazepam is relatively low. Following intraperitoneal injection, the median lethal dose (LD_{50}) for mice is 620 (410-930) mg/kg, and for rats 720 (600-864) mg/kg.[29] These LD_{50} values are higher than those for chlordiazepoxide and diazepam.[22]

Signs of toxicity

Like other benzodiazepines, common signs of toxicity of phenazepam are CNS depression, impaired balance, amnesia, dizziness, loss of coordination, slurred speech, confusion, drowsiness, blurred vision, ataxia, muscle hypotonia, tachycardia (or bradycardia) and both auditory and visual hallucinations.[40,50-53] However, unlike those caused by other benzodiazepines, the toxic effects of phenazepam may last for up to 5 days after ingestion,[16,53] or up to 3 weeks after ingestion,[54], and may fluctuate.[16] In 61 cases that were reported in Sweden over a period of 18 months, 14 (23%) of the 61 patients experienced symptoms for more than 5 days after ingestion, with CNS depression lasting up to 3 weeks. Table 2 shows the results of a systematic study in Russian children aged 11-14 years who presented with phenazepam poisoning.[51]

Table 2. Blood concentration of phenazepam (mg/L) and its associated features of toxicity in children aged 11-14. Adapted from reference 51.

Blood level (mg/L)	Features of toxicity
2.50 ± 1.55	Somnolence, normal pupils, normal skin colour
2.65 ± 0.95	Initial ataxia
2.76 ± 0.98	Tachycardia, muscle hypotonia
3.25 ± 0.55	Deep sleep
4.02 ± 0.3	Coma

Mutagenicity

Phenazepam (dose of 1 mg/kg) administered to mini pigs throughout the period of organogenesis did neither have an embryotoxic nor a teratogenic action,[55] nor does it have an adverse effect on fetal development in rabbits.[56] Phenazepam did not induce chromosomal aberrations as assessed in human lymphocytes of phenazepam treated patients [See reference no. 58 in Brambilla *et al*.[57], which refers to a paper in Russian by Seredenin *et al*., 1980.

DUID (driving under the influence) cases following phenazepam consumption

Benzodiazepines impair car driving.[58] Phenazepam levels in forensic (driving under influence) samples in four driving arrests with CNS impairment in Wisconsin, USA ranged from 0.380 to 5.00 mg/L,[17,59] more than 50 times the therapeutic range of 0.02–0.06 mg/L.[45] Phenazepam cases (n=11) of impaired drivers in Georgia (USA) between March 2010 and August 2011 were investigated by Stephensen *et al*.[60] In five cases only phenazepam was detected and in six cases multiple drugs were detected in addition to phenazepam. Concentration of phenazepam in blood ranged from 0.04 to 3.2 mg/L (median of 0.17 mg/L, mean of 0.50 mg/L). The effects observed in the drivers where symptomatic of central nervous system depression with slurred speech, lack of balance, slow reactions, drowsiness and confusion. Of 4007 confirmed drug cases among apprehended drivers in the U.S., 141 cases were positive for phenazepam (3.5%). The median (range) phenazepam blood concentration was 0.061 mg/L, but had a wide range (0.004-3.600 mg/L). The median

phenazepam concentration in cases with no concomitant stimulant use (that is cases where phenazepam is typically taken to manage the come-down effects of stimulant use) was significantly higher than the overall median concentration.[61] In the U.S., one case of a 24-year-old male driver who was apprehended for impaired driving following the use of phenazepam (0.076 mg/L in blood; no other drugs detected) was reported by Kerrigan *et al*.[62] The subject exhibited slurred speech and profound psychomotor impairment as he needed assistance to prevent him from falling.

In 2003 in Finland, phenazepam was shown positive in 20 drug-impaired cases (reported range 0.018 – 0.4 mg/L).[17] In England and Wales, phenazepam was confirmed 13 DUID cases. In three cases phenazepam was assayed and the levels were 0.12, 0.18 and 0.87 mg/L of blood.[63] Between July 1, 2010 and June 30, 2011 the prevalence of phenazepam in Finland was assessed among drivers apprehended for driving under the influence of drugs), in medico-legal autopsy cases and in police confiscations of illicit drugs.[61] In Finland, 83 cases of such cases were positive for phenazepam (median blood concentration 0.098 mg/L; (range 0.005-3.00 mg/L). In four of these cases (blood concentrations 0.023-3.00 mg/L) aberrations and functional disorders were found to be exclusively due to phenazepam.[64]

Fatal cases following phenazepam consumption
The combined use of benzodiazepines with other CNS depressants, such as opioids and alcohol, increases the risk of respiratory depression and death.[65-68] Phenazepam has been detected in post mortem blood samples of fatally injured drivers in Norway between 2006 and 2008[69] and in Finland in 2008 and 2009.[70]. One 18-year-old teen died and 3 friends hospitalized following use of phenazepam[71] and another fatal cases related to the co-use of phenazepam with opioids[19] have been reported from the USA. Possibly, in the latter case phenazepam alone contributed to severe cardio-pulmonary distress. A fatality due to acute intoxication from a large overdose of phenazepam was reported from Latvia.[40] Nine UK fatalities were reported in men and women aged 31 to 45, in which phenazepam was detected in post-mortem toxicology but not implicated in the cause of death. In seven cases, opioids were responsible for the death and in two cases, cause of death was related to the use of other drugs [72]. Some became semi-conscious after ingesting phenazepam.[73,74] Two fatal cases directly involving phenazepam were notified by Corkery *et al*.[75,76] In 27 out of 29 cases the range of femoral blood phenazepam concentrations was 0.007 to 0.36 mg/L (median 0.097 mg/L), and the cause of death was not directly related to phenazepam. In the other two cases (phenazepam concentration in femoral blood 0.97 mg/L and 1.64 mg/L) phenazepam was either a contributing factor to, or the certified cause of death. The analysis of phenazepam and 3-hydroxyphenazepam in this study suggested that they are unlikely to be subject to large post-mortem redistribution and that there is no direct correlation between tissues/fluid and femoral blood concentrations.[13]

Table 3. Serum concentrations in four fatal cases.[54]

Case	Phenazepam mg/L	Morphine mg/L	Codeine mg/L	Alcohol µg/L	Reference
I	2.52	0.36	0.38	60	[75]
II	0.386	0.116	0.085	-	[19]
III	11.6	-	-	-	[40]
IV	0.22*				[76]

* Additional substances found: methadone 0.65 mg/L, diazepam 0.1 mg/L and nordiazepam 0.21 mg/L

The concentration of case I is greater than that in a non-fatal intoxication (386 µg/L) reported by Mrozkowska *et al*.[54] (cf. Table 3), and is also higher than those reported in forensic driving cases.[17,59,64] The coroner concluded in case I, II and IV that the combined effects of the opiates with those of phenazepam were more than sufficient to cause death.[75] The misuse of phenazepam increases in Turkey and is available now in almost all Turkish provinces.[77] Five young people were admitted in a critical condition to the intensive care unit of the hospital, after taking the substance. In Turkey, three young people have died of the consequences of the use of phenazepam (not further documented).[77]

An analytically confirmed intoxication related to phenazepam (42-year old man) was reported by Dargan *et al*.[78] The victim was transported to the Emergency Department because of the patient's ongoing confusion and disorientation following use of phenazepam (blood level 0.49 mg/L; no other drugs were detected). In Scotland in 2013, phenazepam was found present in 72 post mortem cases (16% of total cases) which was higher than in 2012 (5%) and phenazepam related deaths were more prevalent among those aged 35 and over.[79] The Scottish National Drug Related Death Database (NDRDD) collects a wide-range of data relating to the nature and circumstances of individuals who have died. In Scotland, phenazepam was implicated in or potentially contributed to the cause of death in 34 deaths in 2013, an increase from 12 deaths in 2011 and 19 deaths in 2012, respectively. [80] Note that such involvement does not imply phenazepam as cause of death. Moreover, in 11 of the 12 phenazepam-related cases in 2012, an opioid was found as well. [81] The concentrations reported in blood in the 19 post-mortem cases in Scotland between 2009 and 2011 were between 8 mg/L and 1200 mg/L. No drug concentrations were given for individual cases, but in two cases phenazepam was stated as a contributing factor in the case of death. In one, phenazepam was the sole cause of death.[82]

In Scotland during the period 2010–2014, 228 cases were identified in which phenazepam was detected in post mortem femoral blood. In two of these cases, the cause of death was attributed to solely phenazepam.[83] Case number 1, a 46-year old man with a history of chronic alcohol abuse, was found dead at home. He had no significant injuries and early bronchopneumonia histologically. Case number 2 was a 26 year old man with a history of amphetamine, ecstasy and alcohol abuse, found dead at home. In 54 cases, death was considered as drug related and caused by a combination of phenazepam (range <0.005 to 0.9 mg/L; median 0.10 mg/L) and one or more other drugs, mostly opioids and other benzodiazepines. In 83 cases, death was drug related (frequently heroin or methadone detected) with phenazepam (range 0.005–0.46 mg/L; median 0.05 mg/L) detected but not included in the cause of death. In 89 cases, death was not drug related but phenazepam was present and not included in the cause of death.

The Edinburgh and Lothians Drug-related Death Case Review Group reviewed 79 cases in 2013. Phenazepam was implicated in 5 (2012) and 6 (2013) designated 'multi-drug' fatal cases.[84] The UK National Programme on Substance Abuse Deaths' reported five deaths linked to phenazepam in the year 2012, and nine fatal cases in 2011.[76,85]

In 17 autopsy cases, phenazepam was found in blood. Median level was 0.048 mg/L (0.007-1.6 mg/L). Phenazepam was not considered by the medico-legal team to be the sole cause of death in any of the cases, the majority of them being accidental opioid overdoses.[61]

In post-mortem samples of cases involving illicit drugs in Norway (15-64 year old individuals), diazepam and flunitrazepam were the most frequently found substances in the benzodiazepines – hypnotics group. They were found in 39% and 25% of cases, respectively. The prevalence of phenazepam was only 1%.[86] The frequency of phenazepam in medico-legally examined drug deaths in Denmark (188 total cases), Finland (162 total cases), Norway (194 total cases) and Sweden (255 total cases) was 2.7%, 1.2%, 1% and 0.8%, respectively.[87]

Phenazepam was detected in 3 out of 103 cases (3%) of admitted or suspected recreational drug intoxications in mostly young subjects (78% were ≤ 25 years, and 81% were males) presenting at emergency departments in Sweden. These three (single-agent) intoxications with phenazepam (nasal intake, two men and one woman, aged 17 – 24 years) occurred all in a small town in the central Sweden. The reported clinical effects included drowsiness, slurred speech, ataxia and somnolence.[88] Phenazepam was detected in the seized sample consumed in an accidental case of intoxication after nasal administration of a mixture of butylone, phenazepam and cocaine.[52] Another case involved a young female found dead at home in Norway. Toxicological analysis in autopsy revealed AH-7921 (0.33 mg/L), methoxetamine (0.064 mg/L), etizolam (0.27 mg/L), phenazepam (1.33 mg/L), 7-aminonitrazepam (0.043 mg/L), diazepam (0.046 mg/L), nordiazepam (0.073 mg/L), and oxazepam (0.018 mg/L) in blood. The cause of death considered was AH-7921 in combination with other psychoactive drug.[89]

In the USA, the National Forensic Laboratory Information System (NFLIS) found phenazepam in three cases in 2008. The number of seizures peaked at 97 reports in 2011 and then fell to 64 reports in 2013. From 2008 to 2013, a total of 284 cases related to phenazepam from 31 states were reported.[90]

Other
Luzhnikov *et al*. (2010) reported that the most frequent causes of poisoning occurring in children in Moscow were benzodiazepine related, mainly phenazepam.[51] In 2008, the number of such benzodiazepine related cases reached 15.9% of all children admitted to the Moscow Pediatric Toxicological Center compared to 9.7% in 2001. The highest incidence of benzodiazepine intoxications (up to 46%) was registered in children of older school age.[51] In 20 children (11-14 years of age), phenazepam concentrations were determined in blood. Concentrations higher than 4 ng/ml were associated with initial coma.[51] One case of delirium was reported to be induced by phenazepam.[91] The victim was a heavy poly-drug user and claimed that he had smoked marijuana, consumed two tablets of oxycodone and 2–3 tablets of hydrocodone-acetaminophen, consumed an unknown quantity of lisdexamfetamine, and drank 2 shots of liquor and a bottle of 'Zannie' (containing phenazepam). The Swedish Poisons Information Centre assessing the acute toxicity of phenazepam reported that 14 of 61 (23%) of hospitalized patients experienced symptoms even five days post-ingestion.[53]

6.   Adverse reactions in humans
Adverse reactions of phenazepam include amnesia, dizziness, diminished coordination, drowsiness, blurred vision, slurred speech, and ataxia. Deaths by respiratory arrest due to its misuse in combination with other sedatives have been reported.[76] At high doses, delirium and psychosis-like behaviour have been reported.[91]

7.   Dependence potential

A.   Animal Studies

Phenazepam (2 mg/kg), given in a single dose, had a distinct anti-aggressive effect and depressed the performance of the conditioned maze reflexes.[26] After long-term (30 days) administration of phenazepam, the animals became tolerant to these effects of phenazepam. Withdrawal of the drug led to the development of a 'rebound' ('ricochet') syndrome, characterized by reversal of the anti-aggressive and sedative effects of the drug. Furthermore, 24 or 48 hours after the last dose of phenazepam the adequacy of their response to test stimuli and the performance of the conditioned reflex were disturbed (the maze transit time was increased 20-fold). When placed in the maze, the animal assumed strained posture, squeaked, and developed tachycardia and tachypnea. At the same time, the thresholds of the rats' aggressive response were sharply reduced (below control values), and 80% of the animals showed the appearance of spontaneous aggressiveness. Injection of phenazepam into the abstinent animals completely abolished the motor and emotional manifestations of the 'ricochet' (rebound) syndrome.[26] Valproate (Depakine, a GABA-agonist) abolished the behavioural disturbances after cessation of long-term administration of phenazepam in most animals (60%); the stuporose state (a state of lethargy, immobility and diminished responsiveness to stimuli) disappeared, performance of the conditioned reflex was restored, the spontaneous aggression was diminished, and the normal thresholds of the aggressive response were restored. Administration of alpha-methyldopa, which inhibits catecholamine synthesis through inhibition of DOPA-decarboxylase, abolished to a large degree, but less than valproate, manifestations of the withdrawal syndrome and restored the disturbed equilibrium. The restoration of behaviour by valproate and alpha-methyldopa following withdrawal point to a role for GABA-ergic and dopaminergic mechanisms in the development of tolerance and withdrawal syndrome after long-term administration of phenazepam.[26]

Like other benzodiazepines, phenazepam may induce tolerance. Following repeated administration of phenazepam in mini-pigs, muscle relaxation was less and sleep became shallower, indicating the development of tolerance.[8]

B.   Human Studies

In the study comparing the effectiveness of phenazepam and etifoxine in the so-called adjustment disorder, withdrawal symptoms defined as an increase in the score in the Hamilton Anxiety Rating Scale (Hamilton-A) between the 42th and 49th day, was more common in the phenazepam group than in the etifoxine group (26 compared to 3; p <0.001).[37] The decrease of 56% in the etifoxine group and 45% in the phenazepam group was, however, statistically not significant.

Tolerance
Tolerance in humans has not been described for phenazepam, though doses up to 3 to 20-times the normal dose have been reported in clinical practice.[42]

8. Abuse potential

A. Animal Studies

In phenazepam-trained rats, diazepam (5–30 mg/kg, i.p.) dose dependently substituted for phenazepam in the two-lever liquid reinforced operant discrimination procedure, though only in 40% of the rats tested, whereas phenobarbital and buspirone failed to substitute for phenazepam.[34]

B. Human Studies

No studies available

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Phenazepam is a long-acting benzodiazepine developed in the former Soviet Union during the 1970s. It has been in clinical use since 1978, primarily in Russia, to treat epilepsy, insomnia, alcohol withdrawal syndrome, short-term treatment of anxiety disorders (panic attacks), and as premedication prior to surgery as it enhances the effects of anaesthetics while reducing anxiety[45,53,92] and as an anticonvulsant.[72]

10. Listing on the WHO Model List of Essential Medicines

Not listed

11. Marketing authorizations (as a medicinal product)

Ellara Medical Center, Moscow, Russia (Elzepam)
Akrikhin Pharmaceuticals Co, Moscow, Russia (phenazepam)
Dalkhimpharm, Khabarovsk (phenazepam)
Moskhimfarmpreparaty, Moscow (phenazepam)
Tatchempharmpreparaty, Kazan, Russia (Phezipam)
JSC Olainfarm, Latvia (Fenazepam)
Ru pharma (Internet)

12. Industrial use

No data available

13. Non-medical use, abuse and dependence

In general, phenazepam may be used to enhance the euphoric effects of opioids (such as to 'boost' methadone doses), to alleviate withdrawal or abstinence syndromes (such as between heroin 'fixes'), to temper cocaine highs, and to augment the effects of alcohol.
The euphoric effects of phenazepam have led to its recreational use.[50] Phenazepam is not a 'party drug' but is used by subjects who already have ample experience with other drugs such as heroin, methadone and/or other opioids.[42] In Finland, the typical user of phenazepam was a male poly-drug user in his 30s.[61]

Phenazepam is being used to help come down from the action of other substances, as well as for more recreational purposes.[50] In the last decade, phenazepam gained increasing popularity as a recreational drug. In October 2009, the use of phenazepam was reported for

the first time in the UK and half a year later the first admissions to hospitals following an overdose of phenazepam were reported. Similarly, an increase of unauthorized use of phenazepam has been observed over the past few years in the USA, New Zealand, and some European countries, particularly in Scandinavian countries including Finland, Norway, and Sweden.[18,53,61,69]

Phenazepam can be obtained via direct purchase from Internet.[19] Illicit products of phenazepam have been sold in the USA as a powder, as tablets, and spiked in blotters similar to LSD.[93-95] Phenazepam can be taken orally (most common), snorted, inhaled, administered transdermal or rectally, or injected (after crushing the tablet).[96] Recreational users consider a dose of 1 mg phenazepam to be equivalent to 5-10 mg diazepam. Recreational doses are usually in the range 0.5-2.0 mg[59] and sometimes higher.[94,95]

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Using an internet-based questionnaire, Kapil *et al*. (2014) recently found that of 1500 respondents 7.7% (*n* = 116) had misused one or more benzodiazepines and/or Z-drugs in the UK.[97] Phenazepam was reported to be misused by 9 respondents (7.8%).[97] No other epidemiological data about the prevalence of phenazepam misuse, abuse or dependence have been described.

15. Licit production, consumption and international trade

As a medicinal drug, phenazepam is produced and marketed by pharmaceutical companies. Phenazepam, often produced in China, is easily available via the Internet.

16. Illicit manufacture and traffic and related information

Like other medicinal drugs, phenazepam can easily be purchased via the Internet.
In the USA, phenazepam has been sold as an air freshener known as 'Zannie'. The product contained phenazepam as active ingredient. It can be administered by spraying into the mouth. In combination with antidepressants, sleep medication, pain medication, or alcohol it may be fatal.[91]

Confiscations/seizures
The Scottish police seized for the first time phenazepam in October 2008 which was sold as diazepam. In January 2011, warnings to residents were issued in North Wales about drug dealers selling phenazepam as diazepam.[70] A bag containing 0.02 g of phenazepam powder was seized by German police in Baden-Württemberg in March 2011.[70] The Finish police seized 26 batches of phenazepam, some of them consisted of a mixture of phenazepam and stimulant designer drugs.[61] In 2014, the Turkish police confiscated 18 kg Bonzai (containing phenazepam) and drug materials in Istanbul.[98] In New Zealand, phenazepam has been found in products containing synthetic cannabinoids, called 'Kronic'.[99] Phenazepam appeared to be present in a concentration of 1 mg per gram product together with JWH-018, JWH-073, JWH-122, and/or JWH-250).[100] In South Korea, phenazepam was identified in an unknown concentration in a seized herbal mixture, containing two synthetic cannabinoids.[101] The report of ACMD from 2011[67] described that the Forensic Science Service (FSS) has received 118 cases of phenazepam from local forces in England and Wales in the last 2 years totalling 23,090 tablets. Phenazepam was first seen in a submission to LGC Forensics (from

its police customers) in August 2009, consisting of over 1,000 tablets, with two small seizures later that year. In 2010, there have been 9 seizures (one consisting of over 3,700 tablets) and six seizures in 2011. Most of the seizures have been in the form of tablets.[67] In addition to these seizures, Cockery *et al.*[76] reported seizures totalling 260,000 tablets made in 103 separate cases during 2008-2011 by the Scottish Crime and Drug Enforcement Agency.

17. Current international controls and their impact

Phenazepam is not scheduled under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and past national controls

USA
In the USA, phenazepam is currently neither approved as a pharmaceutical medicine,[19,67] nor listed under the Controlled Substances Act. [61]

EU
Phenazepam is not controlled at the European Union (EU) level and not licensed by the European Medicines Agency for use as a medicine. It is currently not scheduled as a narcotic in most European countries.[61]
Individual member states have taken national measures to control it. Phenazepam is controlled in Estonia, Latvia, Lithuania, Moldova[102], Norway, Sweden,[53] and the Republic of Ireland.[103,104] Phenazepam is covered by prescription legislation (only available on a doctor's prescription) in Estonia, Latvia, Lithuania, the Russian Federation[104] and Belarus.[53] See below for details of some individual EU countries.

UK
Phenazepam is not listed in the British National Formulary and has not received marketing authority in the UK (that is it is not a medicine licensed by the Medicines and Healthcare Products Regulatory Agency).[67] Following the UK Advisory Council on the Misuse of Drugs (ACMD) advice, the Home Office imposed a ban (dated 22 July 2011) under the Open General Import License on the importation of phenazepam.[67,105,106] Following the recommendation of the (ACMD), phenazepam is controlled in the UK, like other benzodiazepines (such as diazepam), as a Class C drug since June 2012.

Germany
In July 2013, phenazepam was controlled via List III of the 'Betäubungsmittelgesetz' (BtMG, Narcotics Act).[107]

Estonia
According to Narcotic Drugs and Psychotropic Substances Act, phenazepam is a Schedule IV substance.[108] Schedule IV is the lowest classification of psychoactive substances in Estonia and includes prescription drugs, including other benzodiazepines.[102,109] It appears to be concordant with Schedule IV in the UN Convention on Psychotropic Substances.

Latvia

According to Cabinet Regulation N 35, phenazepam is a Schedule III substance.[102,109] Schedule III is the lowest classification of active psychoactive substances in Latvia and includes prescription drugs, including other benzodiazepines and barbiturates.[102,109]

Lithuania
According to 'The Law on the Control of Narcotic and Psychotropic Substances' phenazepam is a Schedule III substance.[108] Schedule III is the lowest classification of psychoactive substances in Lithuania and includes prescription drugs.[102,109]

Republic of Ireland
Since August 2010, phenazepam falls under the Criminal Justice (Psychoactive Substances) Act of 2010 which makes it illegal to 'sell or supply for human consumption substances which are not specifically prescribed under the Misuse of Drugs Acts, but which have psychoactive effects.'[110]

Sweden
In 2008, phenazepam was classified as a narcotic under the 'The Ordinance on Prohibition of Certain Goods Dangerous to Health'.

Norway
Since March 2010, phenazepam is considered a 'narcotic', in common with most other benzodiazepines. It cannot be prescribed by physicians.[104]

Finland
Phenazepam was classified as a narcotic in Finland in July, 2014.[111]

Russian Federation
Phenazepam does not appear in this list of controlled substances, dated 2008 and is available by a physician's prescription.[104] However, it has been reported that it is available at some pharmacies without a prescription.

Moldova
Since 2008, phenazepam is regulated by 'The Resolution of the Government of the Republic of Moldova No 79' which prohibits the possession of drugs which is considered a 'drug-related crime or a drug-related administrative offence'.[102]

Australia
In Australia, the states of Victoria and South Australia have passed an Analog Act under which phenazepam is a controlled substance (analogue to existent benzodiazepines).

Canada
Phenazepam is not listed in the Controlled Drugs and Substances Act.[112]

China
Phenazepam is not reported to be controlled in China.[50]

India

Phenazepam is not listed among 'narcotics, drugs, psychotropic substances & precursor chemicals' that are controlled.[50]

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Phenazepam belongs to the group of benzodiazepines which are therapeutically used widely and successfully in the former Soviet States. Though more potent than other benzodiazepines, its pharmacological profile is comparable to the profile of classical benzodiazepines.

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