Ethylphenidate (EPH)
Critical Review Report
Agenda Item 4.7

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Summary

Ethylphenidate is a structural analogue of methylphenidate, which is controlled as a Schedule II substance under the U.N. 1971 Convention on Psychotropic Substances. Ethylphenidate is also produced in vivo as a metabolite when methylphenidate and ethanol are ingested together.

Ethylphenidate acts as a dopamine and noradrenaline reuptake inhibitor in vitro, and can be distinguished from methylphenidate by its greater dopaminergic selectivity relative to noradrenergic actions. Ethylphenidate demonstrates effects typical of amphetamine-like stimulants, including tachycardia, hypertension, dilated pupils, agitation and fever. Users on internet forums report tolerance to its effects, leading to a higher drug dose to achieve the same effect and also describe a strong urge to redose.

It has no known approved medical or industrial applications.

Ethylphenidate is being used for nonmedical purposes, although the prevalence cannot be accurately determined. It was first reported to the European Union in 2011 by the United Kingdom and has been seized in a number of European countries and placed under domestic control in several countries. It is currently being sold as a ‘legal’ product and is readily available online. Ethylphenidate use has been associated with a number intoxications and fatalities, including one death attributable solely to use of the drug.
1. Substance identification

A. International Nonproprietary Name (INN)
   None

B. Chemical Abstract Service (CAS) Registry Number
   57413-43-1 (base) [1]
   19716-79-1 (Hydrochloride) [2]

C. Other Chemical Names
   Ethylphenidate
   Ethyl-2-phenyl-2-(piperidin-2-yl)acetate
   (RS) - ethyl 2-phenyl-2-(piperidin-2-yl)acetate
   dl-ethylphenidate
   EPH

D. Trade Names
   None

E. Street Names
   Nopaine, gogaine, ching, burst, blue, magic crystals, psyclone [3-5]

F. Physical Appearance
   Coarse white, off-white, or yellowish crystalline powder [6]

G. WHO Review History
   Ethylphenidate has not been previously pre-reviewed or critically reviewed. The current review is based on information that ethylphenidate is clandestinely manufactured, poses a public health risk and has no therapeutic use. There is existing published literature that ethylphenidate may cause harm.
2. Chemistry

A. Chemical Name

IUPAC Name: ethyl 2-phenyl-2-piperidin-2-ylacetate [1]
CA Index Name: Not available

B. Chemical Structure

![Chemical Structure Diagram]

Free base:
Molecular Formula: C_{15}H_{21}NO_{2}
Molecular Weight: 247.3327 g/mol

C. Stereoisomers

Ethylphenidate is a chiral compound and is mainly found as the racemate *dl*-ethyphenidate [7]

D. Methods and Ease of Illicit Manufacturing

Ethylphenidate can be produced by hydrolysing methylphenidate with hydrochloric acid (HCl) to ritalinic acid, which in turn, can subsequently be esterified to ethyphenidate with ethanolic HCl (refer to figure below). [8, 9]

![Chemical Reaction Diagram]

E. Chemical Properties

Melting point: Unknown
Boiling point: Unknown
Solubility: Unknown
F. Identification and Analysis

Several non-enantioselective [10-12] and enantiomeric [13] liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays have been reported for the analysis of ethylphenidate in human plasma. Other analytical techniques and assessments of ethylphenidate include Infrared Spectroscopy (FTIR), Gas Chromatography/Mass Spectrometry (GC/MS), Nuclear Magnetic Resonance Imaging (NMR), Proton-Transfer-Reaction Mass Spectrometry (PTR-MS), UFLC-MS/MS. [8, 14-16]

3. Ease of Convertibility Into Controlled Substances

Ethylphenidate can be converted into methylphenidate and vice versa. Methylphenidate is controlled as a Schedule II substance under the U.N. 1971 Convention on Psychotropic Substances.

Ethylphenidate can be produced from methylphenidate as described in Section D. Ethylphenidate is also produced as a metabolite from the co-ingestion of methylphenidate and alcohol (ethanol). [3] This has been confirmed in studies where healthy volunteers received a single oral dose of methylphenidate (20mg) followed by consumption of ethanol [10, 11]. It has been suggested that the formation of ethylphenidate in vivo and its subsequent effects may contribute to the co-abuse of methylphenidate and ethanol. [10]

Ethylphenidate can be relatively easily converted into methylphenidate using methanol and other readily available chemicals. [9]

4. General Pharmacology

A. Routes of administration and dosage

According to internet forums, the most common route of use is by nasal insufflation. [6, 17] Other routes include oral, anal, vapour inhalation and intravenous injection. [6]

B. Pharmacokinetics

There are no controlled human studies of the pharmacokinetics of ethylphenidate. User reports suggest that following its administration the mean onset time is approximately 13 minutes (ranging from 0-35 minutes) for nasal insufflation and 23 minutes (5-31 minutes) for oral administration. The mean duration of effects is relatively short at approximately 2 hours. [17]

The metabolism of ethylphenidate has been investigated in vitro using human liver microsomes and cytosol. Ethylphenidate first undergoes hydroxylation forming two primary mono-hydroxylated metabolites and then secondary metabolites result from
dehydration and ring opening with an additional hydroxylation. The involvement of different human cytochrome P450 (CYP) enzymes was also investigated using a panel of human recombinant CYPs. The results suggested that CYP2C19 is the most important enzyme in ethylphenidate metabolism, with involvement in the formation of all seven detected ethylphenidate metabolites; however, other CYPs also play some role.[18]

C. Pharmacodynamics

Two early studies suggested that ethylphenidate was pharmacodynamically similar to methylphenidate, but less potent. Portoghese and Malspeis [19] reported that ethylphenidate was 80% as active as methylphenidate in inducing locomotor activity in mice. Schweri et al. [20] found that ethylphenidate exhibits approximately 50% of the potency of methylphenidate in the inhibition of \(^{3}\text{H}\)methylphenidate binding to rat synaptosomes.

More recent research has indicated that ethylphenidate is a selective and potent dopamine uptake inhibitor and that this activity resides almost solely in the \(d\) enantiomer. [7, 21, 22]; \(d\)-ethylphenidate shows greater potency than cocaine in dopamine uptake inhibition and, compared to cocaine and methylphenidate, it is more selective for the dopamine transporter relative to the noradrenergic and serotoninergic transporters. \(d\)-ethylphenidate increases locomotor activity and, at high doses, induces stereotypy. For locomotor activity, it is slightly less potent than \(d\)-methylphenidate, possibly due to its relatively low noradrenergic activity.

There are no human studies of ethylphenidate pharmacodynamics.

5. Toxicology

There appear to be no published controlled studies on the safety of ethylphenidate in animals or in humans. Adverse reactions determined from case studies and user internet forums are detailed in the section below.

6. Adverse Reactions in Humans

Three cases of ethylphenidate acute toxicity requiring hospitalization have been reported in the UK [23]. These cases were associated with signs and symptoms similar to other amphetamine-type stimulants, including tachycardia, hypertension, dilated pupils, palpitations, fever, anxiety, agitation, paranoia and tremor.

In a review of reports on user internet forums, ethylphenidate was described as producing a range of adverse effects similar to other amphetamine-like stimulants. These included increased heart rate, sweating, muscle tension (sometimes manifested as jaw clenching, teeth grinding or tremor), decreased appetite, insomnia, agitation and restlessness, anxiety, paranoia, hallucinations and impaired thinking. [6]
Ethylphenidate was first associated with a death in Germany in 2014, but its role in the fatality is unclear. [16] The autopsy indicated death due to mitral valve endocarditis in combination with pneumonia, and it was likely that the endocarditis had persisted for a period before death. It was suggested that the cardiovascular actions of ethylphenidate may have contributed to death, but the concentration in femoral blood (0.1 mg/L) post-mortem was in the lower range found in fatalities.

Ethylphenidate was subsequently identified in a case series of 19 deaths that occurred between July 2013 and December 2014. [3] The majority of individuals were male (n=14) and from the East of Scotland (n=16). Current or previous heroin abuse was a common factor in 16 cases, with injection identified as the common route of administration. The concentration of ethylphenidate in post-mortem femoral blood ranged from 0.008 mg/L to over 2 mg/L. Other drugs commonly detected were benzodiazepines (n=15), methadone (n=8) and other opioids (n=11). Ethylphenidate was specifically mentioned in the cause of death for 5 cases, but there were no cases in which ethylphenidate was the sole cause of death.

The most recent report is of a case series of 7 documented deaths that occurred between February 2013 and January 2015 in the UK in which the presence of ethylphenidate was analytically confirmed. [2] The causes of death were hanging (2 cases), mixed drug toxicity (4 cases) and ethylphenidate toxicity (1 case). The concentrations of ethylphenidate in post-mortem femoral blood ranged from 0.026 mg/L to 2.18 mg/L. In the one case in which ethylphenidate was present as the sole drug and was the apparent cause of death, the concentration was 2.18 mg/L.

7. **Dependence Potential**

   **A. Animal Studies**

   There are no published animal models of ethylphenidate effects.

   **B. Human Studies**

   There are no published reports with ethylphenidate under controlled conditions reporting physical dependence associated with administration of ethylphenidate.

   There is one very brief published case study describing a 24 year old French male who developed dependence on ethylphenidate purchased from the internet. The subject had previously been dependent on cannabis, heroin/morphine and had occasionally used stimulants. [24]
In the review of user reports [6], there was a strong theme of risk of addiction from ethylphenidate use. Users described persistent impulses to redose, urges to prolong the effects, an inability to control craving for the drug and failed attempts to restrain use.

8. Abuse Potential

A. Animal Studies

There are currently no published animal models of ethylphenidate abuse liability using drug discrimination, conditioned place preference or self-administration.

B. Human Studies

There were no published reports of controlled studies evaluating abuse-liability procedures such as self-administration, drug discrimination, or using drug liking inventories.

However, the assessment of user reports [6] described a number of desirable effects of the drug. Users reported an immediate and intense rush of pleasurable stimulation, which was characterized by alertness and a general mood lift. Other effects included increased self-confidence, improved ability to focus and concentrate, and enhanced social interaction and social skills. The pro-social effects appear similar to those reported by users of MDMA.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

There are currently no known therapeutic applications for ethylphenidate.

10. Listing on the WHO Model List of Essential Medicines

Ethylphenidate is not listed on the WHO Model List of Essential Medicines (19th List).

11. Marketing Authorizations (as a Medicinal Product)

None

12. Industrial Use

Ethylphenidate has no current legitimate industrial, cosmetic, agrochemical, cosmetic, human or animal use. It may be used as a reference standard in a forensic laboratories.

13. Non-Medical Use, Abuse and Dependence

Ethylphenidate use has been associated with deaths due to mixed drug toxicity, and in one documented instance, the drug alone. [2, 3] It has been identified in confiscated material e.g. [25], sold over the internet [24, 26] and discussed on drug-user websites. [27-29] Its use has been noted in a number of countries. An internet snapshot survey in 2015 identified 83
websites selling ethylphenidate, with 61% of these based in the UK and the remainder in Europe, Asia and North America. [17] In the UK, it first appeared as a new psychoactive substance (NPS) in 2011 and is now one of the most commonly encountered stimulant NPS. [30]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. **Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence**

Problems documented to date in relation to the use of ethylphenidate are consistent with the actions and effects of an amphetamine-like stimulant. Based on this, as well as user reports and documented cases of toxicity, it would be expected that use of ethylphenidate will be particularly associated with adverse effects on mental health (including paranoia, psychotic effects, anxiety, depression) and risk of potentially fatal cardiovascular disorders.

Some problems have been noted in relation to the route of administration used. The most common route of use is by nasal insufflation and it has been reported that this can be associated with intense pain, nosebleeds and tears [2, 17]. In addition, ethylphenidate injections have been associated with severe soft tissue infections in a series of 9 cases in the UK. However, there were a number of confounding factors, including the presence of other drugs and substances (e.g. citric acid) in the injection solution, contamination and poor injection technique, which make it difficult to assign a role to ethylphenidate itself. [4]

Concern has also been raised over existing drug injectors, particularly heroin injectors, moving to administration of NPS such as ethylphenidate. A survey conducted in the UK suggests that a change to ethylphenidate administration leads to significant adverse effects on physical and mental health along with an increase in risky behavior (e.g. sharing equipment, infection transmission), with a resultant increased demand on health services. [31]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. **Licit Production, Consumption and International Trade**

None

16. **Illicit Manufacture and Traffic and Related Information**

Ethylphenidate, in tablets and powder form, has been seized in a number of countries including France [32], Germany [16], UK [5, 30] and Italy [25].
Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. **Current International Controls and Their Impact**
   Ethylphenidate is not controlled under the 1961, 1971 or 1988 United Nation Conventions. Structurally, ethylphenidate is a homologue of methylphenidate, a stimulant used in the treatment of attention deficit hyperactivity disorder (ADHD) which is controlled as a Schedule II substance under the U.N. 1971 Convention on Psychotropic Substances.

18. **Current and Past National Controls**
   Ethylphenidate is under control in the following countries [23]: United Kingdom (2015), Germany (2013), Denmark (2013), Poland (2015), China (2015), Austria (2012) and Sweden. It is also covered by analogue legislation in a number of countries due to its similarity to methylphenidate.

   Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. **Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance**
   None
References


Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 44 Member States (4 AFR, 2 EMR, 24 EUR, 7 PAH, 1 SEAR and 6 WPR) answered the questionnaire for Ethylphenidate (EPH). Of these, 21 respondents (16 EUR, 2 PAH and 3 WPR) had information on this substance.

LEGITIMATE USE

There were 20 countries that reported no approved medical products containing EPH for human or veterinarian indications. There was also no reported industrial use in 16 countries.

EPH is currently being used in medical or scientific research in one country for metabolism and abuse potential research. Importation is the origin/source of EPH when used for legitimate non-medical/non-scientific use.

EPH was not reported to be used for any cultural, religious or ceremonial purposes in 18 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 16 countries that reported EPH as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are oral (8 countries), sniffing (6 countries), injection (4 countries), inhalation (3 countries) and smoking (3 country). The main route of administration for EPH was reported as oral (3 countries), sniffing (2 countries), smoking (1 country) and injection (1 country). One country commented that it was “through the nose”.

The most common formulation reported for non-medical/non-scientific purposes was powder (13 countries), followed by tablets (5 countries), liquid or solution for oral administration/use (3 countries) and injectable (2 countries) formulations. Other formulations reported were EPH impregnated plant material (2 countries) and tobacco (1 country).

There were 12 countries which reported that the source of EPH for non-medical/non-scientific use was smuggling.

Party settings (1 country) and former/current injectors of heroin (1 country) were specified as subpopulations known to misuse EPH.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (1 country), substantial (4 countries) or serious (5 countries). For the countries that indicated a substantial or serious level of negative health-impact, they specified that it was due to the association of EPH with adverse effects (including intoxications,
transmission of communicable diseases through injection drug use for example large number of soft tissue infections which can result in prolonged hospital admissions and extensive surgical interventions) and fatalities. It was also commented that EPH has mild amphetamine-like side effects and is related to methylphenidate which has been reported as addictive.

Three countries reported emergency room/department visits related to the non-medical use of EPH. A combined total of 2 cases in 2012 and 19 cases (no further information or time frame) were provided.

The adverse effects which presented for EPH at the emergency room/department included hypertension, pupil dilation, mouth dryness, high pulse, elevated body temperature, restlessness, hallucinations, seizures, palpitations, chest pain, fever, drowsiness, anxiety, paranoia, visual disturbance, agitation, bilateral intention tremor and paresthesis. Increased urea and creatine kinase were also listed.

In regards to the mortality rate, data was provided by 4 countries. The rate which included involvement of other substances was reported to be 26 cases in 2013, 9 cases in 2014 (in 7 cases EPH was not reported as cause of death), 9 cases in 2015 and 2 cases in 2016 to date. Finally the rate, where it was unknown if other substances were involved was 19 cases in 2015 and 6 cases in 2016 to date. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

**STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL**

There were 17 countries reported that EPH was under national control. The legislation the control is based upon included Medicines Act (2 countries), Controlled Substances Act (11 countries), Criminal Law Act (1 country), Analog Act (1 country) and other specific legislation (2 countries stated that it was specific legislation for new psychoactive substances). In one country, the control is a temporary provision, ending in June 2017 and it was commented that it will likely become permanently controlled following that. There were no challenges to implementing controls for EPH reported.

The scope of the controls includes production (14 countries), manufacturing (15 countries), exporting (15 countries), importing (17 countries), distribution (16 countries), use (12 countries) and possession (14 countries).

Reported illicit activities involving EPH include manufacture of the substance by chemical synthesis (1 country), trafficking (9 countries), smuggling (1 country), diversion (1 country), domestic internet sales (1 country), internet sales from abroad (7 countries), internet sales from unknown locations (4 countries) and finally sales to people who use this substance (5 countries).

There were 13 countries which completed the section on the number of seizures. The combined number of seizures was 584 (2014), 670 (2015) and 80 (2016 to date). One country stated that EPH has been seized since 2012. Also, one country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.
If EPH was placed under international control, 20 countries responded that they would have the capacity to enforce the control at the national level. There were 20 countries, which responded that they would have the forensic laboratory capacity to analyse the substance.