PRESCRIPTION AND NON-PRESCRIPTION DRUGS USE IN AIRCREW

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Samenvatting

Titel : **Prescription and non-prescription drugs use in aircrew**
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Vraagstelling: Het project maakt deel uit van het Fit-to-Fly Programma, dat in opdracht van de Inspectie Verkeer en Waterstaat, dienst Luchtvaart, wordt uitgevoerd door TNO-TM. In dit rapport worden de volgende vragen beantwoord: 1) is het noodzakelijk voor vliegers een preventieprogramma te implementeren om het gebruik aeromedisch gevaarlijke geneesmiddelen te voorkomen? 2) hoe dienen de vliegveiligheidsaspecten van geneesmiddelen te worden onderzocht? 3) is behandeling van ernstige depressie met selectieve serotonine re-uptake inhibitors (SSRI's) toe te staan voor actieve vliegers?
Werkwijze: analyse van de relevante internationale wetenschappelijke literatuur en analyse van de eigen database, waarin o.a. resultaten van een enquête onder een groep Nederlandse vliegers.
Resultaten: 1) een aanzienlijk aantal actieve vliegers gebruikt voorgeschreven of zelf aangeschafte medicatie, die niet toegestaan is volgens de richtlijnen van de JAR-FCL. 2) Van vele geneesmiddelen zijn de consequenties voor de vliegveiligheid onvoldoende onderzocht. 3) Hoewel de aeromedisch belangrijke bijwerkingen van SSRI's beheersbaar lijken, blijft de ziekte waarvoor de SSRI's worden voorgeschreven (ernstige depressie) een potentieel gevaar voor de vliegveiligheid, wegens de niet-optimale effectiviteit van de SSRI's en de kans op sluipende -moeilijk te herkennen- symptomen.
Conclusie: 1) de resultaten bewijzen de noodzaak een preventieprogramma te implementeren om vliegend personeel en artsen bewust te maken van de specifieke vliegveiligheidsrisico's van geneesmiddelen. Wij bevelen aan om een 'medicatie module' op te nemen in het preventieprogramma, dat door de TNO-TM zal worden ontwikkeld in het kader van de preventie van risicovol alcohol- en drugsgebruik.. 2) bij onderzoek naar de aeromedische consequenties van geneesmiddelen moeten effecten op alertheid, vigilantie en complexe informatieverwerking objectief worden onderzocht onder de hypobare omstandigheden, die heersen in een vliegtuigcabine. Wij bevelen aan om hiervoor een protocol te ontwikkelen, dat is gebaseerd op het protocol dat reeds is ontwikkeld door TNO-TM.
3) vliegers met ernstige depressie dienen niet actief te worden ingezet voor vliegtaken, ook al worden ze behandeld met SSRI's.

Summary

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Purpose: This project is part of the Fit-to-Fly Program, which includes projects on alcohol, drugs, medication, lifestyle, sleep and alertness. The present report answers the following questions: 1) is there a need for prevention of harmful medication use by aircrew? 2) how should flight safety consequences of newly developed medical treatments be assessed?, and 3) is treatment with selective serotonin re-uptake inhibitors (SSRI's) for major depression permissible for active pilots?
Methods: analysis of relevant scientific literature and analysis of the database of our questionnaire survey among a group of Dutch pilots.
Results: 1) a considerable number of active pilots use prescription and/or OTC medication, that is disqualifying for flying duties, according to the JAR-FCL requirements. 2) Flight safety consequences of many treatments have not been sufficiently assessed.3) While aeromedically significant side-effects of SSRI's seem manageable, the disease for which SSRI's are prescribed (major depression) is a potential threat to flight safety due to non-optimal efficacy of SSRI's and the potential for insidious unrecognized symptoms.
Conclusion: 1) the results evidence the need for a prevention program to increase awareness of aircrew and medical practitioners about specific flight safety risks associated with medication. It is recommended to include a 'medication module' in the prevention program, which will be developed by TNO-TM in the context of prevention of harmful use of alcohol and psychoactive drugs. 2) Adequate assessment of aeromedical consequences of medication should include objective testing of alertness and vigilance, and complex information processing under hypobaric conditions prevailing in the aircraft cabin. It is recommended to develop a protocol based on the existing protocol of TNO-TM. 3) Pilots with major depression should be grounded, irrespective of SSRI treatment.

CONTENTS

1. Introduction

The Manual of Civil Aviation Medicine of the International Civil Aviation Organization (ICAO, 1985) states that 'No person shall pilot an aircraft, or act as a flight crew member of an aircraft, while under the influence of intoxicating liquor or any narcotic or drug, by reason of which his capacity so to act is impaired'.

In the United States, the use of psychoactive substances is regulated in the Federal Aviation Regulation (FAR) 91.17:
No person may act or attempt to act as a crew member of a civil aircraft:
-While using any drug that affects the person's faculties in any way contrary to safety.

The legislation of medication and drug use in aviation in the Netherlands is incorporated in the new Dutch Aviation Act (Wet Luchtvaart, 2001) that came into force on 1 September 2000. This law applies to all personnel involved in air traffic operations in the Netherlands, including air traffic control. With regard to substance use the law states that:

Art.2.11 The holder of a pilot certificate shall not perform any duties within the limitations of the certificate when the physical or mental state of the holder is such that he causes or is able to cause harm to the safety of air traffic.

Art.2.12.–1 A member of the aircrew shall not perform any duties on board of an aircraft while he is under such influence of a substance (…)

Aircrew have the ultimate responsibility to comply with above-mentioned regulations, which seem to be clear but not at all detailed. In most cases, aircrew is unaware of the specific flight safety risks of medication prescribed by their treating physician. For their part, most prescribing physicians are unaware of the specific conditions and tasks in aviation and give pilots the same information on side-effects as they give to a 'general' patient, not considering specific risks for flight safety. This may (and in practice does) result in pilots flying, while using medication that is potentially harmful to flight safety.

Moreover, for a considerable number of treatments no data are available on possible adverse effects in the context of flight safety. This applies in particular to a number of recently developed treatments for chronic diseases and prophylactic drugs. At present, patents on newly developed drugs expire rapidly, therefore manufacturers wish to market their products as soon as possible. To gain time, they omit specific tests to assess effects on performance relevant for the transport sector. Many drugs are 'aeromedical orphans', of which the therapeutic efficacy and clinical safety usually are established

and aviation safety is unknown. This particularly applies to safety aspects of recently developed treatments for depressive illness, smoking, benign prostate hyperplasia, erectile dysfunction, diabetes mellitus, and malaria prophylaxis.

The present report will deal with:

1. Magnitude and characteristics of the problem: what is the prevalence of (possibly harmful) use? Is there a problem? If yes, how can we prevent harmful use?
2. Assessment of flight safety consequences of newly developed medical treatments: recommendations for a protocol.
3. As an example of new generation treatments with considerable aeromedical consequences, use of serotonin re-uptake inhibitors for the treatment of major depression will be discussed. This example was chosen in consultation with the Aeromedical Section of the Ministry of Transport, because currently this treatment is a major issue in international discussions in the context of medical certification of pilots.

2. Prevalence and prevention of harmful medication use

All medication, which is incompatible with flying duties, has at least one of the following direct or indirect effects:

- impairment of central nervous system functions (e.g. cognitive and psychomotor performance, vigilance and alertness, consciousness)
- impairment of autonomic nervous system functions (e.g. regulation of circulation, accommodation (eye), metabolism, gastro-intestinal and urinary function)
- impairment of sensory function (e.g. vision, auditory function, vestibular function)

When medication is used for a disease or symptom, which in itself is incompatible with flying duties (e.g. epilepsy, pulmonary infection, cardiac arrhythmia, etc.), flying duties are precluded no matter what the medication may be. This applies to a majority of prescription drugs. In these cases, aviation safety aspects are easy to determine, as disqualifying conditions are clearly defined in the JAR-FCL requirements (JAA, 2002).

Aviation safety issues are an important point of concern with the category of medication used to alleviate a condition, which is not disqualifying for flying duties. This category includes treatments for common cold, allergic rhinitis, diarrhoea, fever and pain, hypertension, insomnia, and prophylactic drugs (e.g. malaria prophylaxis). Both pilots and physicians are often unaware of the specific flight safety risks of the treatments. For most treatments, aviation safety issues have never been assessed. In some cases, car-driving performance has been assessed. However, environmental conditions and the characteristics of tasks in car-driving differ considerably from flying an aircraft. Moreover, there is considerable inter-individual variation in effects of medication on cognitive performance. Conclusions of pharmacological studies are based on group predictions. However, when a pilot is the only one of 100 subjects who experiences adverse effects after taking his medication, he increases the accident risk.

Prevalence of medication use during flying duties

Data on prevalence of medication use during flying duties are scarce, because there have been no large epidemiological studies. Pilots have to report any use of medication during their mandatory periodical aeromedical examinations. However, practice has learned that in many cases temporary use of medication or self-medication (OTC) is not reported or denied. For the same reason, data of the few available surveys may be underestimating the prevalence.

Canfield, Hordinsky, Millett et al. (2000) of the Forensic Toxicology Research Section of the Civil Aeromedical Institute performed a retrospective study on the frequency of all drug and alcohol use in

fatal civil aviation accidents in the United States, which occurred between 1994 and 1998. Data from this study were compared with data from an earlier 5-year study for the years 1989 to 1993 to determine changes in drug use among pilots.
It is noteworthy that prescription drugs were found in 14% (1994-1998) and 6% (1989-1993) and over-the-counter medication (OTC) in 18% and 11.2% respectively. In this study, no causal relationships between accident and drugs use were sought. Results of the 1994-1998 study are summarized for non-recreational drugs in table 1.

Table 1: Fatal Aviation Accidents with medication 1994 to 1998

Pilots (class)	Sedative drugs % (#)	Prescription drugs % (#)	OTC drugs % (#)
airline (1)	2 (4)	7 (18)	15 (36)
commuter (2)	2 (12)	11 (69)	19 (118)
private (3)	3 (25)	18 (136)	19 (144)
Total	**3 (41)**	**14 (223)**	**18 (297)**

Above-mentioned US results on fatally injured pilots are difficult to translate to living European pilots. Highest rates for medication use were found in the group of private pilots. In the US, private pilots form a large and very heterogenous group, incomparable to European private pilots. Moreover, as the results concern fatally injured pilots, they may not be applicable to all pilots, due to selection bias.

Survey among short-haul charter pilots
In a recent survey of the TNO-TM Aviation Medicine Group among Dutch short-haul charter pilots, 22.5% of 160 respondents used one or more prescription drugs while on flying status (Simons, unpublished data). Ten (6.3%) pilots used more than one drug and 22 cases (13.8%) concerned medicaments that are potentially harmful to flight safety and disqualifying according to the JAR-FCL requirements (JAA, 2002). Twelve respondents (7.5%) used a hypnotic during working periods, most of them occasionally. Hypnotics that were used are temazepam (9 pilots), midazolam (2 pilots) and homoeopathic drugs (1 pilot). Besides prescription drugs, OTC self-medication was used by 37.5% of the pilots, while in 5% this OTC medication was potentially harmful to flight safety.

Conclusion

The study by Canfield et al. (2000) covered fatally injured US pilots and the survey of the TNO-TM Aviation Medicine Group concerned a small group of Dutch pilots of one airline. Therefore, applicability of the results to all European pilots may be limited. However, the results of the survey show that in a considerable number of cases pilots use prescription and/or OTC medication, that is disqualifying for aircrew, according to the JAR-FCL requirements (JAR-FCL, 2002). The fact that a considerable number of respondents (13.8%) used treatments that are possibly harmful to flight safety indicates the need to increase awareness of medical practitioners and aircrew about specific flight safety risks associated with medication. For this purpose, a module on medication should be included in the aircrew prevention program, which will be developed in the context of prevention of alcohol and psychoactive drugs use (Simons, 2003). Awareness courses should start already at flying schools and should also be provided to ground personnel engaged in safety-sensitive activities.

In addition, medical practitioners should be informed about the principles of aviation medicine. This may be achieved through dissemination of information in the medical press and through short courses on aviation medicine.

Furthermore, as the flight safety consequences of many relevant treatments have not been sufficiently assessed, a standard protocol for such assessments should be developed. Recommendations for such protocol are discussed in section 3.

3 Assessment of flight safety consequences of medical treatments

Piloting modern aircraft requires complex psychomotor co-ordination, high rates of information processing, and high-speed decision making. On the other hand, during prolonged operations, pilots have to sustain attention and to maintain vigilance under relatively monotonous conditions. These capacities are particularly vulnerable to the cognitive side-effects of drugs. During the last 10 years, tools have been evaluated and developed to assess pilot's performance during operational duties. The Vigilance and Tracking task (VigTrack; Valk, 1994) and the Multi-Attribute Task battery (MAT) developed by NASA (Comstock & Arnegard, 1992), were identified as the two tasks tapping both sides of the pilot workload spectrum. In laboratory studies both performance tasks were successfully applied to demonstrate detrimental (residual) effects of alcohol and sedative effects of various antihistamines as well as residual effects of hypnotics under conditions of simulated cabin pressure in a hypobaric chamber (e.g. Valk, Simons, Struyvenberg et al., 1997).

The effects of drugs on performance may be aggravated by the effects of cockpit environmental factors, such as lower ambient pressure. Ambient pressure in the cabin of modern aircraft ranges between 81.2 and 75.2 kPa, which corresponds with atmospheric pressures at altitudes between 6000

and 8000 ft. It has been shown that this lowered pressure causes mild hypoxia (oxygen saturation of haemoglobin 89-93%; Simons and Krol, 1996), which may affect performance and may facilitate or potentiate possible performance impairing effects of drugs. Therefore, subjects should be exposed to cabin pressure (75.2 kPa) during test sessions. Tests should include a vigilance and tracking task, such as the VigTrack, and a complex information processing task, such as the MAT.

Above-mentioned recommendations apply to assessments for the civil commercial transport industry. For military pilots, assessments should include additional tests addressing lower atmospheric pressures, acceleratory forces, such as positive and negative Gz, and disorientation stimuli.

4 Serotonin re-uptake inhibitors

The discussion on the use of serotonin re-uptake inhibitors for the treatment of major depression is an important issue in the aeromedical approach to medication and flying, because this concerns treatment for a disease, which in itself may be incompatible with flying duties with drugs that may have harmful side-effects. Serotonin re-uptake inhibitors are presently widely prescribed as anti-depressants. Because they have less harmful side-effects than the older tricyclic anti-depressants, some aeromedical consultants in Canada, Australia, and USA are considering approval of these drugs for treatment of pilots remaining on flying status (Lange, 2002; Hudson, 2002; Emonson, Wilkins, Sweeney and Ross, 2002, Ireland, 2002).

Depressive illness is one of the most frequent psychiatric disorders with a lifetime prevalence of 5-10% (NHG, 1996). As opposed to a rare episodic event, emerging literature characterizes major depression as a recurrent or chronic disease (Glass, 1999; Hirschfeld and Schatzberg, 1994). In the general population, patients whose first major depression is in full remission, statistically face up to an 85% chance of recurrent depression within 15 year (Mueller, Leon, Keller et al., 1999).
Currently, aircrew receiving treatment for depression are grounded for the full duration of pharmacologic treatment followed by at least 3 months observation. Denial of medical certification is based on 1) depressive disorder is a disqualifying condition, and 2) the side-effect profile of anti-depressant medication. If an ideal therapy existed, with 100% efficacy and no side-effects, pilots treated for depressive illness could remain on flying status. The possibility to remain on flying status, may further contribute to recovery.

Based on their side-effects profile, anti-depressants are subdivided in classic tricyclic anti-depressants (TCA's) and non-tricyclic anti-depressants. Due to their side-effects profile, use of classic tricyclic anti-depressants is clearly disqualifying for pilots (JAR-FCL, 2002), therefore this category will not be discussed in the context of this report. Non-tricyclic anti-depressants include serotonin re-uptake

inhibitors (SRI's), selective serotonin re-uptake inhibitors (SSRI's), and other non-tricyclic compounds, such as mianserin, mirtazapin, and moclobemide, which is a monoaminooxidase inhibitor. Only the group of SSRI's will be discussed as possible treatment for pilots, because the other non-tricyclic anti-depressant's side-effect profiles are established and unacceptable for pilots.

SSRI's include the following compounds:

scientific name	*trade name®*
citalopram	Cipramil
fluvoxamine	Fevarin
fluoxetine	Prozac
paroxetine	Seroxat
sertraline	Zoloft
venlafaxine	Efexor

Of this group, fluoxetine and sertraline are most frequently used. The major effect of these drugs is to inhibit the re-uptake of serotonin from the neuronal synapses, the net effect of which is to increase serotonin levels in extra-cellular fluid. Increased synaptic serotonin levels inhibit the firing rates of terminal axons in a feedback inhibition mechanism (Petty, Davis, Kabel and Kramer, 1996). SSRI drugs were initially marketed for major depressive disorder and are presently also prescribed in the management of panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder (DeVane, Liston and Markowitz, 2002), pre-menstrual syndrome, body dysmorphia, eating disorders, aggression-impulsive disorder, Raynaud phenomenon, migraine headaches, premature ejaculation, chronic pain, fibrositis, fibromyalgia, and chronic fatigue syndrome (Ireland, 2002). They are becoming increasingly popular and are presently prescribed to cope with various frustrations of everyday life in a modern society.

4.1 Efficacy

Major depressive disorder is the main target condition for SSRI drugs. The aim of treatment is to normalize mood and other characteristics of depression, such as loss of interest and guilt feelings. For SSRI's, as well as for tricyclic anti-depressants, this effect is first noticeable after 2-4 weeks of treatment. Serotonergic anti-depressants, such as some TCA's and all SSRI's also have an anxiolytic action, which is also first noticeable after 2-4 weeks. It is generally accepted that TCA's are as efficacious as SSRI's with regards to above-mentioned aim of treatment (e.g. Anderson, 1998; Muijsers, Plosker and Noble, 2002). Except for severe depression, where TCA's appear to be more

efficacious than SSRI's. In the context of efficacy, SSRI's have no advantages over TCA's, but SSRI's are to be preferred because their side-effects profile is clearly more favorable than that of TCA's.
To assess severity of depression and therapeutic efficacy, validated rating scales are used, such as the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967), which is the scale most frequently used in literature. The most frequently used criterion for efficacy is the percentage of 'responders'. 'Response' is defined as at least 50% decrement in the HDRS-score after 6 weeks of treatment. In placebo-controlled studies, the percentage responders varies between 40-65% for most anti-depressants and from 25-55% for placebo (Anderson, 1998). Taragano, Lyketsos, Paz et al. (1999) found a full remission in 52% of 469 patients with mild-to-moderate depression after 8 weeks of treatment with sertraline. Keller, Kocsis, Thase et al. (1998) found a major depression recurrence rate of 6% in a 76-weeks sertraline trial with middle-aged adults (placebo: 23%).
From these data, it is clear that efficacy is not 100% and a significant number of patients will keep depressive symptoms in spite of anti-depressant therapy.

Although the HDRS, by providing numerical values for feelings, is useful as a tool in efficacy studies, it may be less useful for clinical judgement of the individual disease status. It is very difficult, even for experienced psychiatrists, to assess the state of mood of depressive patients or, for instance, to predict suicidal actions. It is generally known that anti-depressant treatment increases the risk for suicide in the first weeks of treatment of severe (vital) depression.

4.2 Side-effect profile of SSRI drugs

Acute side-effects
The acute side-effect profile of the SSRI's is generally characterized by potentiation of serotonin: gastro-intestinal complaints (nausea, diarrhea, constipation), (migraine-like) headache, anorexia, agitation, insomnia, and increased bleeding tendency. Other side-effects are somnolence, tremors, dizziness, tachycardia, sexual dysfunction, and effects on the autonomous nervous system, such as dry mouth and increased perspiration (Mauri, Laini, Cerveri et al., 2002, Farmacotherapeutisch Kompas, 2002, Haddjeri, Blier, de Montigny et al., 1999).

SSRI's not only inhibit re-uptake of serotonin in the neurons, but also in other cells, such as thrombocytes. This leads to impaired aggregation of thrombocytes with consequent higher bleeding risk. In a large case-control study, de Abajo, Rodriguez and Montero (1999), found a 3-fold increased risk for upper digestive tract hemorrhages in patients using SSRI's. The level of risk is comparable with the risk for digestive tract bleeding found for ibuprofen, a non-steroidal anti-inflammatory drug.

Sertraline and other SSRI's have been associated with hypoglycemia (Pollak, Mukherjee and Fraser, 2001), hepatotoxicity (Carvajal, Garcia, Sanchez et al., 2002), and lowering of the seizure threshold, although sertraline appears to have a relatively low risk for seizures (Pisani, Oteri, Costa et al., 2002).

SSRI's have also been associated with prolongation of QTc interval and torsades de pointes, but the only reports of torsades de pointes appeared to occur with mirtazapine (which is not a SSRI) and multiple studies found no effect or reductions in QTc interval produced by sertraline, citalopram, and paroxetine (Goodnick, Jerry and Parra, 2002).

To get insight in the frequency of the most common side-effects, Haddjeri et al. (1999) studied patients with moderate uncomplicated depression and using the SSRI sertraline, or bupropion (not reported here), or placebo for 8 weeks. The results are presented in table 1. It is noteworthy that 30-40% of both groups of patients complained about headache. This illustrates that studies of side-effects of anti-depressants are hindered by the fact that the depressive illness may in itself be associated with several complaints.
Reactions severe enough to interfere with flight safety that persist more than 2-4 weeks are likely to continue longer (Ireland, 2002).

Table 1. Profile of common side-effects of sertraline compared to placebo (Haddjeri et al., 1999)

side effect	*sertraline* (n=120) %	*placebo* (n=120) %
headache	36	32
nausea	31	10
diarrhea	26	11
insomnia	18	4
somnolence	17	6

It is concluded that the acute side-effect profile of SSRI's necessitates grounding of pilots for the initial phase of treatment. Steady-state levels for longer acting SSRI's, such as fluoxetine, may not be achieved for 70 days. Aeromedically, this would require a minimum waiting period of at least 2-3 months on medication before allowing a flier to resume aircrew duries, irrespective of clinical outcome of the condition treated, in order to have some assurance toxicity would not develop.

Persistent side-effects

Cognitive performance impairment is a potential and aeromedically relevant side-effect of SSRI's. While serotonin agonism itself may improve some cognitive functions, such as memory, other adverse effects may outweigh advantages (Ireland, 2002). The literature on cognitive and psychomotor effects of SSRI's is generally favorable (Lane and O'Hanlon, 1999). The only study using aeromedically relevant cognitive tasks has been conducted by Paul, Gray and Lange (2002), who studied the effects of 5 weeks sertraline treatment in 19 healthy volunteers. While they found some of the expected side-effects of sertraline (sleep problems, increased drowsiness, dry mouth), there was no effect on psychomotor performance. Although tests were not performed under hypobaric cabin conditions, sertraline seems void of harmful effects on cognitive functions. However, the occurrence of side-effects, such as insomnia, drowsiness, and dry mouth preclude safe performance of flying duties. In this context, it is important to realize that dry mouth may indicate ongoing anticholinergic effects that can affect vision and alertness as well.

While not aeromedically relevant as cognitive effects, the most common persistent adverse effect of SSRI's is sexual dysfunction. Treatment of premature ejaculation with SSRI's is based on this side-effect.

Delayed side-effects

A delayed effect of profound aeromedical significance is SSRI-induced mania. SSRI-induced mania can indicate a pre-existing diathesis to bipolarity, which is an unwaiverable psychiatric condition. Symptoms of mania are insomnia, grandiosity (with lack of self-criticism), and extreme irritability. Evolving mania, poses a significant danger to flight safety, as decrements in judgement may not be obvious during the initial onset of this disorder and become manifest while performing flight duties (Ireland, 2002).

Another aeromedically significant delayed effect, which can occur months to years after asymptomatic SSRI use, is the onset of a movement disorder caused by diminished dopamine levels in the striatum as a result of enhancing serotonergic transmission with SSRI's. This may lead to symptoms in the form of involuntary tics (e.g. eyelid) and twitches (e.g. legs). Involuntary movements can threaten safety during critical phases of flight.

Discontinuance effects

When SSRI treatment is abruptly terminated, a flu-like serotonin discontinuance syndrome may occur. Symptoms of the serotonin discontinuance syndrome include dizziness and vertigo, lightheadedness, headaches, confusion, memory difficulties, fatigue, paresthesias, chest tightness, tremor, nausea, anorexia, insomnia, nightmares, cold hands, and sweating (Burry and Kennie, 2000). These symptoms are clearly incompatible with flight safety. The syndrome may occur 12-72 hour after the last dose in the case of short-acting SSRI's and 1-3 weeks after a longer acting SSRI's, such as fluoxetine. In most cases treating physicians will prevent this syndrome to occur by waning a patient gradually off their

medication. However, it is not infrequent in long-term treatment of depression that the patient terminates treatment all by him/herself or forgets to take the medication for several days. Moreover, effects of disturbed circadian rhythmicity, common in pilots, may alter pharmacokinetic profiles, or make pilots to forget to take their medication. However, knowledge on circadian influences on SSRI levels is lacking.

Interactions

Although their effect is much less than that of older tricyclic antidepressants, SSRI's may have inhibitory effects on the major cytochrome P450 enzymes, involved in the metabolism of many drugs. Within the group of SSRI's, differences in inhibitory activity exist: citalopram and sertraline have a low inhibitory activity, while fluoxetine and paroxetine are potent inhibitors (Spina and Scordo, 2002). Through their inhibitory activity on P450 enzymes, co-administration of SSRI's may increase blood levels of various drugs, who are dependant on P450 enzymes for their metabolism. Interactions of special interest include those of SSRI's with alcohol, caffeine, grapefruit juice, herbal preparations, other medications, and cigarette smoke. SSRI's can elevate blood alcohol levels and caffeine levels, while pink grapefruit juice and macrolide antibiotics can elevate SSRI levels. Aviators using -blockers are vulnerable to increased -blockade. Hallucinations and delirium have been observed with combinations of sertraline or paroxetine and hypnotics, such as zolpidem, temazepam, and zaleplon (Bezchlibnyk-Butler and Jeffries, 1999). Ginko biloba used with an SSRI may increase the risk of petechiae and bleeding due to anti-hemostatic effects (Bezchlibnyk-Butler and Jeffries, 1999). Smoking can decrease the metabolism rate of fluvoxamine by 25%. Thus a patient stabilized on fluvoxamine who either quits or starts smoking cigarettes may inadvertently raise or lower fluvoxamine levels, respectively (Ireland, 2002).

4.3 Aeromedical discussion on SSRI's

Currently, most aeromedical authorities do not approve SSRI use by actively flying pilots. However, Canadian and Australian authorities have approved SSRI treatment of selected active pilots under strict supervision with special reference to disease status and aeromedically significant side-effects. In the USA, discussions on limited approval are in progress. Advocates of approval argue that strict prohibition against use of SSRI's by pilots can lead to aircrew flying with symptoms of depression (including impaired cognition), occult SSRI use, and/or aggressive herbal regimens (e.g. Saint John's wort) - all potential threats to flight safety. They further argue that medically supervised use of SSRI's (including neuropsychological cognitive assessments) minimizes the incidence of adverse effects and flight safety risk. Should their use be authorized, those waivered to fly after a psychiatric episode need not to attempt to cover-up or continue flying with recurrent illness in order to retain their profession (Ireland, 2002). The arguments concerning control of adverse-effects may be valid. With a rigorous and frequent medical supervision most cases with aeromedically significant side-effects can be managed or selected out. However, the disease that is treated with SSRI's (major depression) is a chronic disease with a considerable recurrence rate. Also, the percentage responders to antidepressant therapy, either TCA's or SSRI's, varies between 40-65% (Anderson, 1998). Thus a considerable number of patients will keep depressive symptoms in spite of antidepressant therapy. These patients may have aeromedically significant depressive symptoms, which in many cases are difficult to recognize even for psychiatrists.

It is concluded that, while aeromedically significant side-effects of SSRI's seem manageable, the disease for which SSRI's are prescribed is a potential threat to flight safety due to non-optimal efficacy of SSRI's and insidious symptoms, which sometimes can not be reliably recognized.

5 Conclusions

Need for prevention
In a considerable number of cases pilots use prescription and/or OTC medication, that is disqualifying for flying duties, according to the JAR-FCL requirements. The fact that many cases concern treatments that are potentially harmful to flight safety indicates the need to increase awareness of medical practitioners and aircrew about specific flight safety risks associated with medication.

Assessment of flight safety consequences of medical treatments
Flight safety consequences of many relevant treatments have not been sufficiently assessed. Adequate assessment includes objective testing of alertness and vigilance, and complex information processing under hypobaric conditions prevailing in the aircraft cabin at cruise altitude.

Serotonin re-uptake inhibitors for major depression

It is concluded that, while aeromedically significant side-effects of SSRI's seem manageable, the disease for which SSRI's are prescribed is a potential threat to flight safety due to non-optimal efficacy of SSRI's and insidious symptoms, which sometimes can not be reliably recognized.

6 Recommendations

Prevention

A module to stimulate awareness on the flight safety aspects of medication should be included in the aircrew prevention program, which will be developed by TNO-TM Aerospace Medicine Group in the context of prevention of alcohol and psychoactive drugs use. Awareness courses should start already at flying schools and should also be provided to ground personnel engaged in safety-sensitive activities.

In addition, medical practitioners should be informed about the principles of aviation medicine. This may be achieved through dissemination of information in the medical press and through short courses on aviation medicine.

Assessment of flight safety consequences of medical treatments

A protocol should be developed for assessments in the context of aeromedical certification and treatment of pilots. This protocol should be implemented at a European level. It is recommended to develop the protocol in accordance with the protocol that has already been developed for this purpose by TNO-TM Aerospace Medicine Group.

Serotonin re-uptake inhibitors for major depression

Pilots treated for major depression should be grounded for the full period required by JAR-FCL. Although their side-effects seem manageable, use of SSRI's should not change this approach.

7 References

Abajo FJ de, Rodriguez LA, Montero D. (1999). Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ*; 319:1106-1109.

Anderson IM. (1998). SSRI's versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety*; 7(suppl 1):11-17.

Bezchlibnyk-Butler K, Jeffries J. (1999). Clinical handbook of psychotropic drugs. 9th ed. Toronto: Hogrefe & Huber Publishers. p. 3-11.

Burry L, Kennie N. (2000). Withdrawal reactions. Pharmacy Practice 2000; 4:2. http://www.pharmacyconnects.com/content/phpractice/2000/04-00/php040002.html

Canfield D, Hordinsky J, Millett D, Endecott B, Smith R (2000). Prevalence of drugs and alcohol in fatal civil aviation accidents between 1994 and 1998. Office of Aviation Medicine Report DOT/FAA/AM-00/21

Caravajal GP, Garcia D, Sanchez SA, et al. (2002). Hepatotoxicity associated with the new antidepressants. *J Clin Psychiatry*, 63(2):135-137.

Comstock JR., Arnegard RJ. The Multi-Attribute Task battery for human operator workload and strategic behavior research. NASA TM-104174, National Aeronautics and Space Administration, Langley Research Center, 1992.

Devane CL, Liston HL, Markowitz JS. (2002). Clinical pharmacokinetics of sertraline. *Clinical Pharmacokinetics*, 41(15):1247-1266.

Emonson D, Wilkens P, Sweeney R, Ross J. (2002). Letter to the editor. *Aviation Space Environmental Medicine* 73(12):1241.

Farmacotherapeutisch Kompas 2002. A.C. van Loenen (Ed.). Commissie Farmaceutische Hulp van het College voor Zorgverzekeringen, Amstelveen, 2002. p. 109-119.

Glass R. (1999). Treating depression as recurrent or chronic disease. *JAMA,* 281(1):83-84.

Goodnick PJ, Jerry J, Parra F. (2002). Psychotropic drugs and the ECG: focus on the QTc interval. *Expert Opin Pharmacother*; 3(5):479-498.

Haddjeri N, Blier P, de Montigny C, Croft H, Settle E Jr, Houser T, Batey SR, Donahue RM, Ascher JA. (1999). A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther*; 21(4):643-658.

Hamilton M. (1967). Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.*, 6(4):278-296.

Hirschfeld R, Schatzberg F. (1994). Long-term management of depression. *Am J Med*, 97(6A, suppl.):33s-38s.

Hudson DE. (2002). SSRI use in professional aircrew. In Asthma 2002 Meeting extracts. Proceedings of the 73nd Annual Scientific Meeting, Montreal, Canada. Aerospace Medical Association, Alexandria, VA.

ICAO (1985). Manual of Civil Aviation Medicine. Second edition. Doc 8984-AN/895. International Civil Aviation Organization, Montreal, Canada.

Ireland RR. (2002). Pharmacologic considerations for serotonin reuptake inhibitor use by aviators. *Aviation Space Environmental Medicine* 73(5):421-429.

JAA (2002). Joint Aviation Requirements JAR-FCL, Part 3 Medical. Joint Aviation Authorities, Hoofddorp, 2002.

Keller M, Kocsis J, Thase M et al. (1998). Maintenance phase efficacy of sertraline for chronic depression.

JAMA, 280:1665-1672.

Lane R, O'Hanlon J. (1999). Cognitive and psychomotor effects of antidepressants with emphasis on selective serotonin reuptake inhibitors and the depressed elderly patient. *Ger J Psychiatry*, http://www.gwdg.de/~bbandel/gjp-article-lane2.pdf

Lange M. (2002). Maintenance SRI use in professional pilots: the Canadian experience. In Asthma 2002 Meeting extracts. Proceedings of the 73nd Annual Scientific Meeting, Montreal, Canada. Aerospace Medical Association, Alexandria, VA.

Mauri MC, Laini V, Cerveri G, et al. (2002). Clinical outcome and tolerability of sertraline in major depression: a study with plasma levels. *Prog Neuropsychopharmacol Biol Psychiatry*, 26(3):597-601.

Mueller T, Leon A, Keller M, et al. (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry*, 156:1000-1006.

Muijsers RB, Plosker GL, Noble S. (2002). Sertraline: a review of its use in the management of major depressive disorder in elderly patients. Drugs Aging; 19(5):377-392.

NHG (1996). NHG-standaard Depressie. In: S. Thomas (ed) NHG-standaarden voor de huisarts II. Utrecht: Bunge, 1996.

Paul MA, Gray G, Lange M. (2002). The impact of sertraline on psychomotor performance. *Aviat Space Environ Med*, 73:964-970.

Pisani F, Oteri G, Costa C, et al. (2002). Effects of psychotropic drugs on seizure threshold. *Drug Safety,* 25(2):91-110.

Petty F, Davis LL, Kabel D, Kramer GL. (1996). Serotonin dysfunction disorders. A behavioural neurochemistry perspective. J Clin Psychiatry, 57 (suppl 8):11-16.

Pollak PT, Mukherjee SD, Fraser AD. (2001). Sertraline-induced hypoglycemia. *Ann Pharmacother*, 35(11):1371-1374.

Simons R, Krol J. (1996). Jet leg, pulmonary embolism, and hypoxia. *Lancet*; 348:416.

Simons M, Witte JJ. (2003). Recreational drugs and aircrew. Report no. TNO-TM 72173 (draft). TNO-Human Factors Institute, Soesterberg, 2003 (submitted).

Spina E, Scordo MG. (2002). Clinically significant drug interactions with antidepressants in the elderly. *Drugs Aging*, 19(4):299-320.

Taragano F, Lyketsos CG, Paz J, Schapira M, Comesana Diaz E, Klimovsky S. (1999). An open-label trial of sertraline for the treatment of major depression in primary care. *Ann Clin Psychiatry*; 11(2):67-71.

Valk PJL. (1994). The assessment of vigilance under the continuous load of a compensatory tracking task. Netherlands Aerospace Medical Centre 1994, Soesterberg.

Valk, P.J.L., Simons, M., Struyvenberg, P.A.A., Kruit, J., & Van Berge Henegouwen, M. Effects of a single dose of loratadine on flying ability under conditions of simulated cabin pressure. *Am. J. Rhinology* 1997; 11(1): 27-33.

Wet Luchtvaart. (2001). Luchtvaartwetgeving. Luchtvaartwet, Regeling Toezicht Luchtvaart. Bewerkt door mr. H. Scholtens. Editie Schuurman & Jordens 104-II. Zeventiende druk. ISBN 90-140-6800-X Uitgeverij W.E.J. Tjeenk Willink.

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