Risk and Benefit Assessment for Tolcapone in the treatment of Parkinson's disease

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Summary

Objectives
To assess the evidence for the effectiveness and tolerability of tolcapone in the treatment of Parkinson's disease.

Methods
The literature from 1990 to 2003 was searched systematically to identify randomised trials of tolcapone. Search methods included the Roche intranet to find the most up to date safety issues, the electronic database including Medline, PubMed and Web of Science as recommended by Cochrane Collaboration and also a manual search of the major journals in the field.
Eligible patients for the present study were those with fluctuating PD who were being treated with peripheral dopa-decarboxylase inhibitor (DDC-I) L-dopa / beserazide or L-dopa / carbidopa.

Results
Thirteen randomised trials were identified but ultimately only 5 studies met all the criteria for the present study. The efficacy of tolcapone 200 mg three times daily as adjunct therapy to Ldopa/DDC-I was examined. All outcomes of "on" time, "off" time, changes in daily L-dopa dose and Parkinson's disease rating scale showed favourable results for tolcapone compared to placebo, and meta-analysis was able to identify significant improvement from the baseline with reduction in the L-dopa daily dose. In the present study, fixed effects were used when the Q statistic showed no significance. With "on" time increase (hours), the pooled weighted mean difference (WMD) = 1.92 (95% CI = 1.40, 2.45) (fixed effects) (6 week assessment). With "off" time decrease (hours), the pooled (WMD) = -1.83 (95% CI = -2.34, -1.32) (fixed effects) (6 week assessment), the pooled (WMD) = -1.38 (95% CI = -2.05, -0.71) (fixed effects) (12 week assessment). With L-dopa daily dose, random effects was used as the Q statistic was significant, and the pooled weighted mean difference = -168.90 (95% CI = -204.57, -133.24) (random effects) (6 week assessment).
More dopaminergic side effects were reported in the patients randomised to the tolcapone group. Hepatotoxicity appeared after marketing but none of the studies included in the present study considered the results of the liver function test to be significant.

Conclusion
Systematic review provides the most reliable available current evidence from randomised clinical trials. The present study to assess tolcapone demonstrates the hypothesis that the currently most used L-dopa treatment combined with tolcapone prolongs L-dopa efficacy. Most adverse events reported in the studies were managed by reducing the dose of L-dopa. A patient's quality of life is very poor indeed with advanced Parkinson's disease. The cause of hepatoxicity is not clear, but if there is no other effective treatment, it may be worth using tolcapone for the benefits in spite of this risk. However it is essential to keep patients under careful observation when tolcapone is used concomitantly.

Acknowledgements

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My thanks go specially to my husband for all his support and understanding.

CONTENTS

Abbreviations

AADC	Aromatic amino acid decarboxylase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
AST	Aspartate amino transferase
COMT	Catechol-O-methyl-amino transferase
CSM	Committee on the Safety of mMedicine
DA	Dopamine agonist
DDC	Dopa decarboxylase
DDC-I	Dopa decarboxylase inhibitor
DOPAC	Dihydroxyphenylic acid
EMEA	European Agency for Evaluation of Medicinal Product
FDA	Food and Drug Administration
HVA	Homovanilic acid
IGA	Investigators' global assessments
L-dopa	Levodopa
M-H weight	Mantel-Haenszel method
3-MT	3-Methoxytyramine
NTT	Number needed to treat
3 OMD	3-O-methyldopa
OR	Odds ratio
PD	Parkinson's Disease
QOL	Quality of life
RD	Risk difference

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Chapter 1

1 Introduction

Parkinson's disease (PD) is named after Dr James Parkinson, whose most famous work was "An Essay on the Shaking Palsy" written in 1817, which provided a clinical description of this disorder. The clinical features are "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported, with a tendency to bend the trunk forwards". Forty years later "rigidity" was added to the clinical description of PD and the name Parkinson's disease was attached to the syndrome. PD is an age-related neurodegenerative disorder with an average age at onset of 60 years. An estimated 1 million persons in the United States suffer from PD, and there are approximately 60,000 people newly diagnosed each year in the USA (Olanow, 2001). The diagnosis of PD is complex as the symptoms do not only appear in PD patients. Usually it is diagnosed when patients show the presence of two or three cardinal features. MRI examination also supports the diagnosis.

Although progress of the disease is slow with only minor symptoms such as involuntary movement at first, most PD patients eventually have disabilities which affect their daily life such as their speech, walking, and dressing. It becomes very difficult for them to do ordinary things.

The main treatment is L-dopa therapy to replace dopamine. However, the efficacy gradually becomes reduced and the symptoms are not controlled long-term. Therefore, other medications such as anticholinergic drugs or dopamine agonists are used in the early stages of Parkinson's disease. This is why other additional medications such as Catechol-O-methyl-amino transferase (COMT) inhibitors and peripheral dopa

decarboxylase inhibitors have been developed. The present study focuses on one of the COMT inhibitors, tolcapone, which inhibits human erythrocyte COMT activity after oral administration. After clinical trials, there was a high expectation of approximately doubling the bioavailability of L-dopa. This is because of a decrease in L-dopa clearance resulting in a prolongation of the terminal elimination of the half-life of L-dopa, which may lead to a decrease in requirement for L-dopa therapy.

1.1 Parkinson's disease

Parkinson's disease occurs when the neurotransmitters in the brain which mediate movement are defective, and patients therefore experience trembling limbs or slow movement. It can be overlooked, as some patients think the symptoms are due to ageing. The symptoms of Parkinson's disease can be considerably improved by drugs and a careful consideration of life-style.

The cerebrum consists of many neural cells which perform several roles. One of these produces dopamine which is responsible for movement. Parkinson's disease is caused by a decrease in dopamine. As a result, commands from the brain cannot be transmitted properly and patients develop movement disorders or autonomic nervous system disorder. Most patients develop this in late middle age and it progresses as a chronic disease.

1.2 Epidemiology

The disease is a common neurodegenerative disorder that often affects people aged over fifty although some people develop PD before their fifties. A distinction is made between parkinsonism, Parkinson syndrome and juvenile parkinsonism.

It is predominantly older people who develop Parkinson's disease. In a population of young people there would be a low incidence, while in a population of older people there would be a higher incidence. As is clear from the above, PD is an age-related neurodegenerative disorder with an average age at onset of 60 years. PD occurs throughout the world, in people from all classes of society and from all races (Pearce, 1999). Also, men and women are equally afflicted by PD. It is believed that the disease is seldom inherited. Figure 1.1 below shows the incidence of Parkinson's disease related to the age at which it develops.

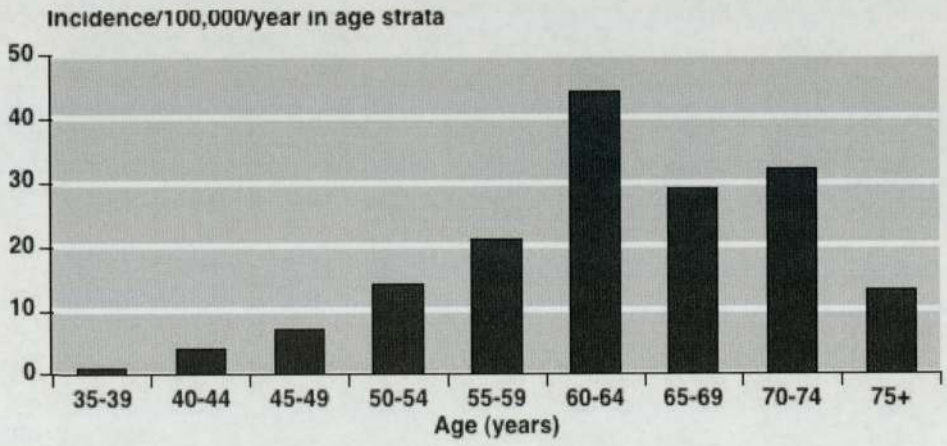


Figure 1.1 Parkinson's disease incidence and age (Adapted from Twelve D et al., Systematic review of incidence studies of Parkinson's disease. Movement disorder 2003; 18; 19-31)

1.3 Aetiology

Parkinson's disease (PD) is a common and disabling condition in the expanding elderly population. The general age at which people develop Parkinson's disease is most commonly in their fifties and next most commonly in their sixties, but some people start to develop it before their forties, and an idiopathic disorder occurring before forty can also be seen.

The onset, symptoms and progress of Parkinson's disease vary considerably between patients. The distribution of idiopathic PD patients of different ages at the onset of PD is shown in Fig 1.2. The etiology of PD remains unknown. Both genetic and environmental factors have been suspected.

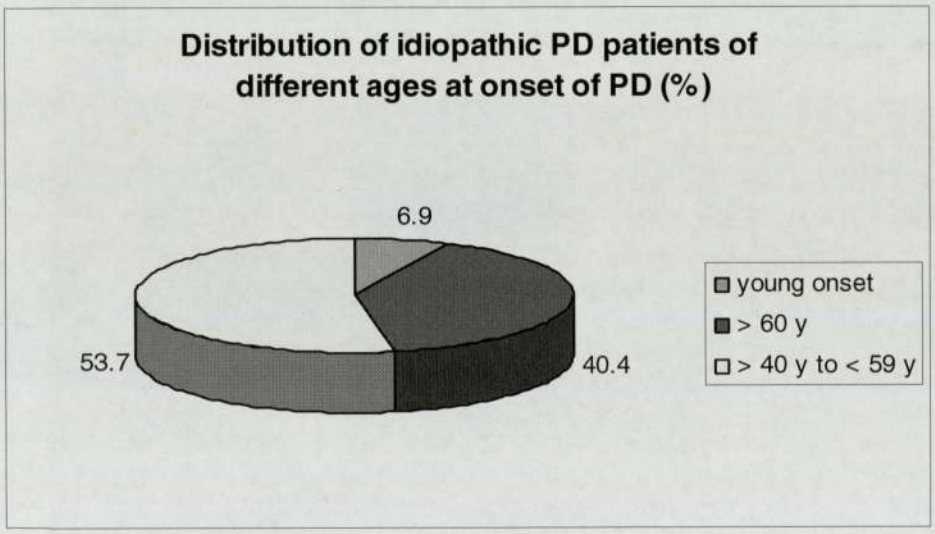


Figure 1.2 Distribution of idiopathic PD patients of different ages at onset of PD (%) (Adapted from Pantelatos A and Fornadi F "Clinical Features and Medical Treatment of Parkinson's Disease in Patient Groups Selected in Accordance with Age at Onset," in *Advances in Neurology*, 1993; Vol 60)

PD is one of a number of very common neurological disorders. Its prevalence increases with age. The figures of age and gender according to research are shown below.

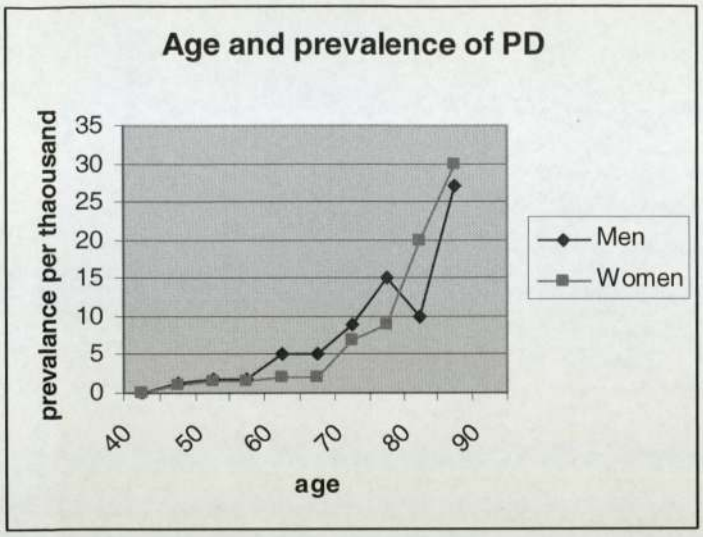


Figure 1.3
Age and prevalence of PD (Adapted from Mutch. W.J et al., British Medical Journal 1986; 292; 534 – 536)

As shown in Figure 1.3, approximately one per 1000 people under the age of 60 develops Parkinson's disease, five to 1000 at the age of 70, and 20 per 1000 over the age of 85. In the 80's, the prevalence of men and women is reversed. The reason for this may be that women have a longer life than men.

1.4 Symptoms of Parkinson's disease

Parkinson's disease has four characteristic symptoms, as listed in Table 1.4.1. In many cases, the first symptom is a tremor in one hand, which later spreads to the other hand and then spread more widely throughout the body. Slowness is one of the early symptoms, as is awkwardness of movement such as in turning in bed, in rising from lying to sitting, and from sitting to standing. The patient's posture and face change in a characteristic way and the neck and trunk are bent. The whole body leans forward and arms and legs may also be flexed at the elbows, wrists, hips and knees respectively. The facial expression becomes immobile. Bradykinesia particularly affects gait; patients find

it difficult to start walking, may be unable to stop walking and may start to run uncontrollably. The performance of movement may show remarkable fluctuations over the day. Many patients experience a phenomenon known as "freezing". Most episodes occur without previous signs, and patients are unable to complete an activity such as walking, writing, or speaking. These episodes usually last for a few minutes on average, although the length varies between individuals. Mentally patients are normal in the early stages of PD but many patients become depressed and dementia often develops in the later stage.

Patients taking L-dopa may experience unpleasant fluctuations known as the "on-off" phenomenon.

TABLE 1.4.1 Symptoms of Parkinson's disease

Motor system symptoms	Ridigity
	Tremor
	Freeze
	Posture abnormality
Autonomic nervous system symptoms	Constipation
	Dysuria (pollakiuria in the night)
	Orthostatic hypotension
	Dyshydrosis
Mental Symptoms	Depression
Others	Listlessness
	Deformation of limbs

(Adapted from Pearce MS. Family Doctor Guide to Parkinson's disease. The British Medical Association, 1999)

1.5 Pathogenesis

The substantia nigra exists in the mesencephalon, and looks black as it contains melanin. In order to move our limbs and maintain a good posture we need dopamine, which is manufactured in the substantia nigra. Dopamine is transferred to the corpus striatum, and the neural transmitter acetylcholine is also in the corpus striatum. When dopamine and acetylcholine are well-balanced, the neural cells work in a well-balanced way and we are then able to move smoothly. Parkinson's disease starts when the substantia nigra and the neural cells in the corpus striatum become reduced. As a result, the dopamine in the corpus striatum is reduced and tremor, rigidity or walking abnormalities start.

As stated above, Parkinson's disease is caused when a lack of dopamine in the corpus striatum is established. Figure 1.4 shows the dopamine transmission pathway and how it is affected by Parkinson's disease. The grey areas show where there is damage and how this affects the flow. L-dopa treatment, the replacement of dopamine, was started, based on the idea that lack of dopamine caused Parkinson's disease. Dopamine does not reach into the brain as it is, so its precursor L-dopa is used. L-dopa changes to dopamine in the brain. As well as dopamine, other transmitters such as serotonin, somatostatin and noradrenaline can be related to Parkinson's disease. The mechanism is becoming clearer and as a result methods of treatment have improved. However, the reason why the substantia nigra becomes impaired is as yet unknown.

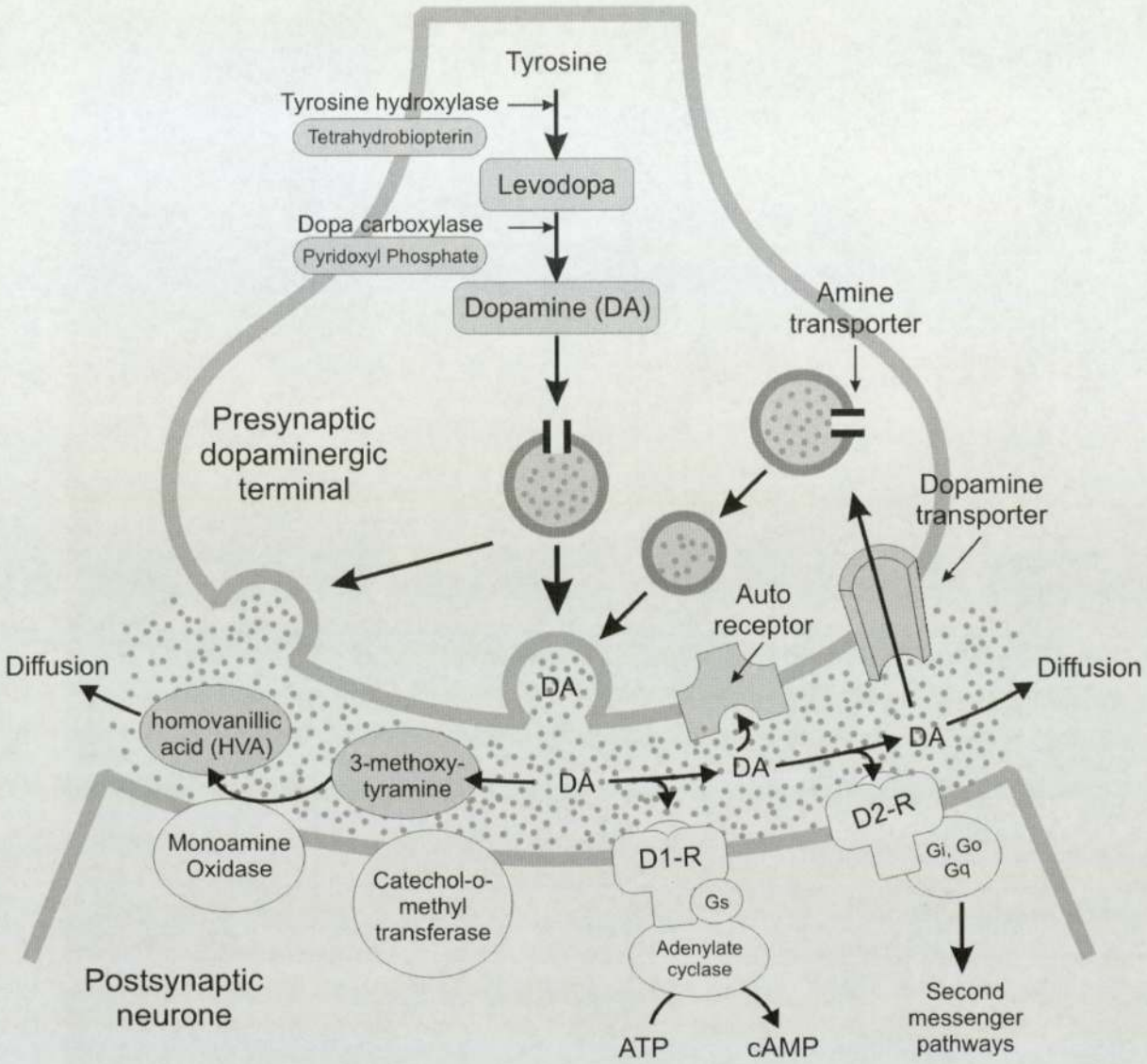


Figure 1.4

Outline of the dopamine transmission pathway illustrating the points affected in Parkinson's disease. Elements shaded grey represent elements of the pathway that are affected in Parkinson's disease.
(Adapted from Parkinson's disease Q & A. Hirai S. Iyaku Journal, 2000)

1.6 Assessment of seriousness of disease/ outcome measures in PD
Measurement of seriousness of Parkinson's disease

1.6.1 Hoehn and Yahr's Staging of Parkinson's Disease

Hoehn and Yahr's staging of Parkinson's disease (Massachusetts Central Hospital, 2004) roughly gives the level of disease progression (Table 1.6.1.1). This scale has largely been supplanted by the Unified Parkinson's Disease Rating Scale which is much more complicated.

Table 1.6.1.1 Hoehn and Yahr's Staging of Parkinson's Disease

Stage 1
- Signs and symptoms on one side only
- Symptoms mild
- Symptoms inconvenient but not disabling
- Usually presents with tremor of one limb
- Friends have noticed changes in posture, locomotion and facial expression

Stage 2
- Symptoms are bilateral
- Minimal disability
- Posture and gait affected

Stage 3
- Significant slowing of body movements
- Early impairment of equilibrium on walking or standing
- Generalized dysfunction that is moderately severe

Stage 4
- Severe symptoms
- Can still walk, to limited extent
- Rigidity and bradykinesia
- No longer able to live alone
- Tremor may be less than at earlier stages

Stage 5
- Cachectic stage
- Invalidism complete
- Cannot stand or walk
- Requires constant nursing care

(Adapted from Functional and Stereotactic neurosurgery Massachusetts Central Hospital Harvard Medical School http://neurosurgery.mgh.harvard.edu/functional/pdstages.htm)

1.6.2 Unified Parkinson's Disease Rating Scale (UPDRS)

This is a scale obtained from observation at interview with the physician. Patients were examined at all visits by the same investigator, who also evaluated the baseline.

The UPDRS was measured and changes in the mean daily levodopa dose were also measured from the baseline to find out if it is better to use tolcapone as an adjunctive in addition to traditional therapy.

The UPDRS consists of subscales I to VI. Details of scoring are given in Appendix 3.

Subscale I: Mentation, Behaviour and Mood

Subscale II: Activities of Daily Living for "on"

Subscale III: Motor Examination

Subscale IV: Complications of Therapy

Subscale V: Hoehn & Yahr Scale ("on")

Subscale VI: Modified Schwab England Scale

1.6.3 The treatment of Parkinson's disease

Table 1.6.3.1 Drug therapy

Typical Symptoms and Disability	Common Treatment
No disability	No drugs or selegiline
Early tremor and rigidity	Anticholinergics and/or selegiline
Stiff and slow despite anticholinergics	Add amantadine or pergolide
Slow, marked tremor, falls, work in jeopardy	Levodopa given with benserazide (Madopar®) or carbidopa (Sinemet®)
Early dyskinesia or fluctuations	Smaller doses, but frequently administered, of pergolide
Late levodopa failure	Long acting benserazide or carbidopa + pergolide, or apomorphine injections

(Adapted from Pearce MS. Family Doctor Guide to Parkinson's disease. The British Medical Association, 1999)

As shown in the above Table 1.6.3.1, L-dopa is usually prescribed when anticholinergic drugs begin to have less effect. L-dopa is successful in treating most of the symptoms of moderate to severe Parkinson's disease. However, the side-effects of L-dopa need to be reduced.

Nausea, vomiting and fainting are known as adverse events in the early stages. At a later stage, the duration of the effectiveness of L-dopa becomes shorter, and this is called "wearing off" at the end of the dose. Dyskinesia and dystonia, "on-off" fluctuations and mental confusion and hallucinations are known at this stage.

1.6.3.1 L-dopa

Dopamine replacement therapy is the most common and effective drug in the treatment of PD as described above. If a patient continues to experience nausea and vomiting with the appropriate dose of Madopar® or Sinemet®, the peripheral dopamine receptor

antagonist metocropramide is given. This can be effective in preventing these adverse events.

Motor complications including dyskinesia and motor fluctuations occur in 50 to 90 % of PD patients with disease progression. This problem occurs in virtually 100 % of patients who have received L-dopa for 5 – 10 years and in patients who develop PD when they are young. In the parkinsonian state, the subthalamic nucleus is more active than in the normal state, leading to increased inhibition of the brainstem and thalamocortical neurons and people thus develop parkinsonian motor complications. By contrast, dyskinesia is believed to be related to a decrease in the subthalamic nucleus. (Olanow, 2001)

1.6.3.2 Dopamine agonist

Dopamine agonists have been known, since the 1970s, as a treatment for PD, and new dopamine agonists have been introduced into the market one after another. Dopamine agonists stimulate the dopamine receptor and improve dopamine function and then the symptoms improve. Recent drugs are different from older drugs in that they are relatively selective in stimulating the dopamine receptor. Well known dopamine agonists are bromocriptine, pergolide, pramipexole, ropinirole, cabergoline and lisuride. Bromocriptine and pergolide stimulate a wider array of nondopaminergic receptors. Bromocriptine is an ergot derivative, which is a D_2 receptor agonist and a weak D_1 receptor antagonist, while another ergot derivative, pergolide, is a D_2 receptor agonist but a weak D_1 receptor agonist and thus differs from bromocriptine.

1.6.3.3 Increased dopamine release

In Parkinson's disease patients, dopamine does not disappear completely. In order to release dopamine, amantadine is used. This is also used as an anti-viral agent for influenza. The mechanism of amantadine in PD has not been established, but it is believed to work by increasing dopamine, by blocking dopamine re-uptake, by stimulating dopamine receptors, and, possibly, by anticholinergic effects. Disadvantages are cognitive side effects and it is relatively ineffective for the more disabling features of PD.

1.6.3.4 Anticholinergic drugs

In the corpus striatum, dopamine and acetylcholine are balanced in healthy people. In patients with PD, however, dopamine decreases and then acetylcholine increases relatively and the balance is upset. In the early stage, anticholinergic drugs are used to balance dopamine and acetylcholine.

1.6.3.5 Monoamine oxidase inhibitors

Monoamine oxidase is an enzyme which decomposes dopamine. Monoamine oxidase inhibitor inhibits this action.

1.6.3.6 Noradrenaline supplementation

When noradrenaline decreases, this leads to a postural disorder, especially shuffling steps. The precursor of noradrenaline converts into noradrenaline and is effective for treating shuffling steps amd dizziness when standing up.

1.6.4 Characteristic symptoms

What is "wearing-off"?

"Wearing off" describes the fluctuation of symptoms owing to the reducing efficacy of L-dopa from the first time of taking the drug. For example, at the beginning of treatment with L-dopa, the symptoms of Parkinson's improve for 6-7 hours, but this is shortened to 2 – 3 hours as time goes on, so the symptoms have worsened by the time the patient next takes L-dopa.

This "wearing-off" phenomenon appears as early as 2 years after starting L-dopa for some people. The frequency increases with the length of treatment and the increased amount of the dose.

What is "on –off"?

"On-off" means that after taking L-dopa, an "off" status happens along with reduction of the effectiveness of L-dopa with the passing of time. "On-off" can happen unexpectedly. This "off" develops regardless of when L-dopa was taken or of the blood concentration of L-dopa. It sometimes appears for a few seconds or minutes as if turned off by an electric switch. The symptoms of Parkinson's disease then suddenly appear. The "off " phase patient shows sudden freezing, feet sticking to the floor and immobility, sometimes with feelings of fear and panic. The mechanism of "on-off" symptoms is still unclear but there is a view that the changing of the affinity of the post-synaptic receptor is related. "On-off" is often seen in patients who have advanced Parkinson's disease. These patients also develop dyskinesia when in an "on" condition. In these patients, usually no movement is seen when in the "off" condition but they develop dyskinesia during the "on" time.

Taking steps to counteract "on-off" is similar to treatments for "wearing-off", but is usually more difficult.

1.7 Tolcapone

Tolcapone, (Tasmer®), is a new drug for Parkinson's disease, which was marketed in 1998 but was withdrawn from most countries apart from the U.S.A in the same year owing to its hepatoxicity, which was identified during post-marketing studies. Figure 1.5 shows the reduction in the use of tolcapone after there had been a warning about hepatotoxicity.

Tolcapone decreases peripheral L-dopa metabolism and prolongs its serum half-life thereby making more L-dopa available for transport across the blood-brain barrier over a long period of time (Davis 1995, Dingemanse 1995). Although, tolcapone was withdrawn in most countries, it is still prescribed in the U.S.A. for limited clinical use and requiring special monitoring for patients with PD on L-dopa/carbidopa, who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies. A few years after its withdrawal from Europe, tolcapone was returned to the market in 2004 for use in Europe. In April 2004, a meeting of the European Committee for Proprietary Medical Products recommended lifting the suspension of the marketing authorization for tolcapone.

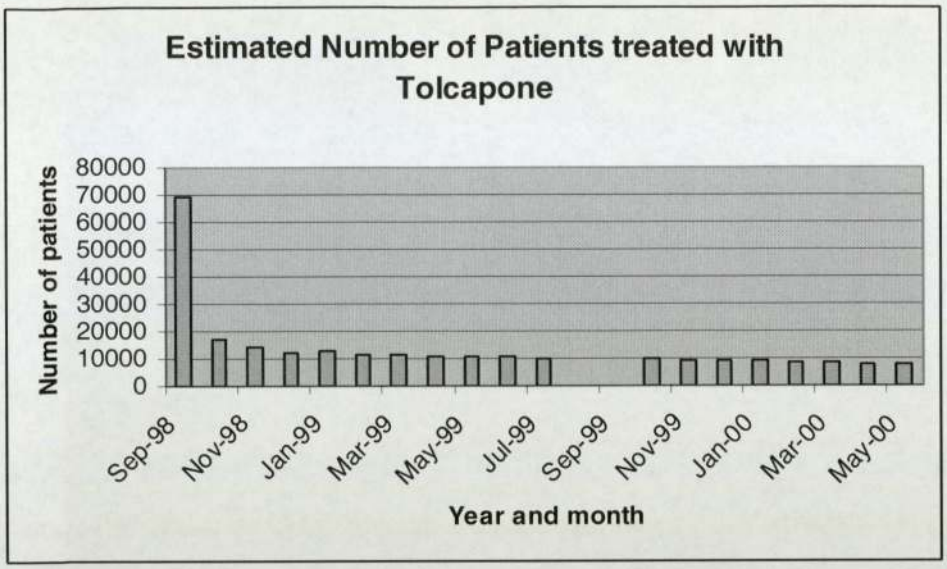


Figure 1.5 Estimated number of patients treated with tolcapone in the world (Adapted from Roche intranet. Tasmar safety update report. Roche, 2000)

1.7.1 Mechanism of action of tolcapone

Figure 1.6 illustrates the mechanism of tolcapone and shows the action of how it inhibits the metabolisation of dopamine.

Tolcapone (3, 4-dihydroxy-4'-methyl-5nitrobenzophenone), is a catechol-O-methyltransferase (COMT) inhibitor which has been developed to improve the pharmacokinetics of L-dopa and is used as an adjunct to combined L-dopa and aromatic amino acid decarboxylase (AADC) inhibitor therapy, AADC is also known as dopa decarboxylase (DDC). In the presence of AADC inhibition, 3-O-methylation of L-dopa via COMT is the most important metabolic pathway, leading to fast elimination of L-dopa, and accumulation of its metabolite 3-O-methyldopa. Therefore tolcapone, as a potent, specific, and reversible COMT inhibitor, increases the availability of L-dopa delivery to the brain.

Tolcapone inhibits catechol-O-methyltransferase (COMT) inhibitors, improves the bioavailability and decreases the elimination of L-dopa, and inhibits the formulation of 3-O-methyldopa (3 OMD). In other words tolcapone thus enhances the therapeutic effect of L-dopa in patients with Parkinson's disease.

Dopa decarboxylase (DDC) inhibitors, benzerazide and carbidopa, have largely eliminated the metabolic pathway for L-dopa and allow the dose of intake to be reduced by about 75 % (Kaakkola, 2000).

However, the penetration of dopamine into the brain is poor. Many drugs have been developed to improve the pharmacokinetics of dopamine and to reduce the increased concentration and the fluctuation of dopamine levels in the plasma. The COMT inhibitor, tolcapone, is one of these.

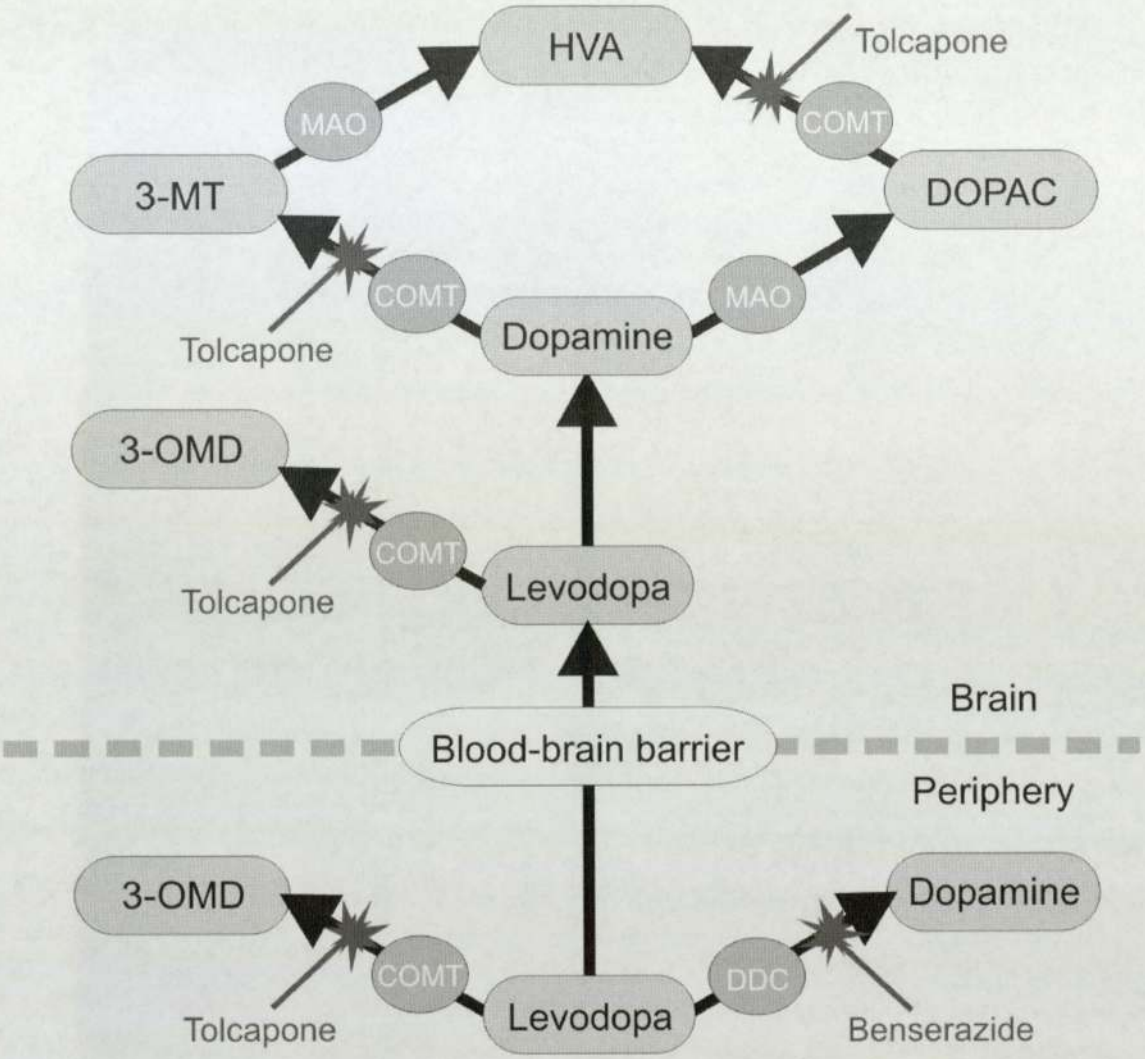


Figure 1.6 Mechanism of tolcapone (Adapted from Kurth and Adler. Neurology 1998; 50 (suppl 5): S3-14)

3OMD: 3-D-Methyldopa,
COMT: Catechol-O-methyltransferase
DDC: Dopa decarboxylase
MAO: Monoamineoxidase B
DOPAC: Dihydroxyphenylic acid
3-MT: 3 methyl-tyramine
HVA: Homovanilic acid

1.7.2 Measurement of the efficacy of tolcapone

The efficacy of tolcapone has to be measured taking into consideration the characteristic symptoms of PD. Tolcapone was developed in order to produce pharmacokinetic advantages such as prolonging L-dopa efficacy in terms of prolonging its half life. The efficacy is measured from the following:

1. Plasma concentrations of L-dopa Cmax
2. Tmax; time to Cmax peak plasma concentration
3. Levodopa AUC
4. Levodopa t1/2
5. Changes in the dose of L-dopa
6. "On" time
7. "Off" time
8. UPDRS score

1.8 Pharmacovigilance

Pharmacovigilance is the ongoing surveillance of product safety throughout a product's life cycle. Adverse events need to be defined and measured throughout the cycle. Pharmacovigilance is of extreme importance for all pharmaceutical companies. For drugs to be effective it is important to be able to balance their therapeutic efficacy (benefit) with their liability to cause harmful effects (risk). Pharmacovigilance by government health agencies is also necessary from a pharmaceutical company's perspective because of its responsibility for ensuring the safety of its products. It is also

necessary to ensure the protection of public health and to inform health care professionals of the risks and benefits of particular drugs as an aid to their decision-making. The US Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) and other agencies have developed sites containing enormous amounts of information both on pharmacovigilance in general and on specific drugs in particular. Under the US 'Freedom of Information Act' the FDA has put major parts of its adverse event database on line. Regulatory documents are also available from the FDA site or from hyperlinks described in the site (Cobert et al., 1999).

Most developed countries have laws to protect public health. This is increasingly managed globally and from an industrial perspective, and regulatory compliance is required. Companies with effective post-marketing surveillance programmes enhance their reputations through increased confidence in their products. The aims of pharmacovigilance will therefore be clarified in this research.

1.8.1 History

The most shocking drug-related tragedy was the thalidomide disaster in 1961. Thalidomide, a sedative drug first synthesised in 1953, was manufactured and distributed by Chemie Grünenthal of Germany. It was subsequently sold in a number of other countries (Schulz, 2001). Thalidomide was prescribed widely because it was considered to be unusually safe – largely because it was almost impossible to commit suicide with it. It was licensed and marketed in Britain and the British Commonwealth (in countries such as Australia, New Zealand, and some countries in Africa by the Distillers Company).

Thalidomide was exceptionally effective in the treatment of morning sickness in pregnancy, but it was found to cause terrible foetal malformations.

The impact was especially devastating in West Germany (4000 affected individuals) where the drug had been sold over the counter (Routledge, 1998). Following the thalidomide tragedy, a Committee on the Safety of Drugs was established by health ministers in the UK to deal with the problem of drug registration. Other countries also became more cautious when approving drugs for marketing, and regulatory bodies were quickly established in many countries.

No drug which is pharmacologically effective is entirely without risk. The risk may be insignificant or may be acceptable in relation to the drug's therapeutic action. Furthermore not all risks can be known before a drug is marketed as neither tests on animals nor clinical trials with patients will always reveal all the possible side effects of a drug. These may only be known when the drug is administered to large numbers of patients over considerable periods of time (Strom, 2000)

1.8.2 Adverse drug events

Adverse Event (AE):

any untoward medical occurrence, which does not necessarily have to have causal relationship with treatment, in a patient or clinical investigation subject, who has been administered a pharmaceutical product.

Adverse drug reaction (ADR):

all noxious and unintended responses to a medicinal product related to any dose (Definition of International Conference on Harmonisation: ICH).

An adverse event (AE) is therefore an undesirable experience occurring to a subject, whether or not considered related to drugs. Adverse events may be unexpected and sometimes unpredictable. They can include a lack of expected efficacy and events related to drug withdrawal. Adverse drug reaction (ADR) is therefore focussed on a causal relationship between a drug and an adverse event. There should be a reasonable possibility that the drug caused the adverse event.

As a rule confirmation of the connection between a drug and an adverse reaction requires further analytical or experimental study (Meyboom et al., 1997)

There are three types of adverse drug reaction. The characteristics of each type of ADR are outlined in the following.

Type A ADRs are the result of an excess of known pharmacological or therapeutic effects of the drug. They are usually predictable, common and rarely life-threatening. They generally occur early in treatment and often disappear with continued administration or when the drug is withdrawn or the dose is reduced.

Type B ADRs have less obvious mechanisms and cannot usually be predicted. They are rare, often serious and sometimes fatal. Type B ADRs may occur at any time during treatment.

Type C ADRs include those ADRs that occur after long-term treatment and are related to duration and dose of the drug.

1.8.3 Systems for collecting information about ADRs

1.8.3.1 Spontaneous reporting

Spontaneous reporting is the most common method used in pharmacovigilance and generates signals for new or rare ADRs (Alvarez-Requejo et al., 1998).

The sources of spontaneous data are healthcare professionals, consumers, lawyers and the literature. Spontaneous reporting, unlike other surveillance techniques, is available immediately a new drug is marketed, continues indefinitely and covers the entire patient population receiving the drug. Until recently Europe, including the UK, received information only from health professionals, whereas the US received information from consumers as well (Kennedy et al., 2000) (Wiholm et al., 2000). However, information now also comes from private individuals in the UK (MHRA, 2004).

Problems in reporting safety data:

Direct reporting from doctors allows relevant details about the case to be established. There are advantages for the doctors in getting advice on whether a reaction has been seen previously. Information about ADRs is reported to the regulatory authorities and is then passed on to the manufacturer. However such information may be delayed and incomplete. The first barriers to the reporting of adverse reactions directly to the manufacturers are ethical dilemmas. Doctors who suspect an adverse reaction to a particular drug may feel that the patient's trust is being betrayed, and particularly that confidentiality is compromised, if the reaction is reported to a third party. Secondly, there is no legal requirement in the UK for doctors to report adverse reactions. The doctors may be anxious that the information which is to be reported could be used in a court of

law to his or her disadvantage, for example as an admission of liability in a civil case alleging negligence. Conversely, there may be concern that by reporting an ADR to the company, the doctor might in some way compromise the patient's case if damages were subsequently to be claimed against the manufacturer. Other barriers to reporting may be that the doctor may decide that it is unnecessary to duplicate a report of the adverse reaction by reporting to both the Committee on the Safety of Medicine (CSM) and the pharmaceutical company. To some extent, the doctor may feel exposed to criticism from the company for the way that the clinical problem has been handled. The doctor may fear that he will be bothered with repeated requests for detailed information. If the doctor is considering publication of a case report, he or she may worry that the company might apply coercion to try to prevent this from happening. In some countries, e.g. France, reporting to the regulatory authority is mandatory (Adams et al, 1991).

Limitations of spontaneous data

Spontaneous reports given to companies are anecdotal and data is not always collected systematically. It is therefore difficult to determine what has occurred and causality determination is complex and imprecise in distinguishing between the drug and the course of the disease because of incomplete information.

Also many external factors influence the data such as the age of the product, external interest (consumers, media, lawyers), the seriousness of the event versus the seriousness of the disease, and the likelihood of the event.

ADR reports on same source reports cannot be used for comparative data.

1.8.3.2 Clinical Study

In order to introduce any new medicine to the market, the pharmaceutical companies will have spent many years in development. First of all, drug toxicity studies are held in animals, followed by 4 stages of clinical studies and each study provides its safety data about the drug.

Determining whether any observed toxicity is serious enough to warrant further development requires pre-market risk-benefit analysis, dose response estimation of toxicity effects, assessing reproductive toxicity and teratological potential and assessing clinical safety. The use of clinical trials to identify adverse events is routine in the process of drug development. Phases I to IV involve clinical trials in humans.

Phase 1: Trials are usually conducted on just a few healthy volunteers. The exception to this is where the drugs are so toxic that it would not normally be considered ethical to expose healthy individuals to them. Examples are cytotoxic drugs. The aims are to determine the metabolism of the drug in humans and to exclude any common toxic reactions.

Phase 2: Trials are generally conducted on a small number of patients who have the target disease. Usually this is the first time the patients are exposed to the drug. The aims are to obtain more information on the pharmacokinetics of the drug and on any relatively common adverse reactions, to obtain initial information on the possible efficacy of the drug, and to determine the daily dosage and regimen, which are then evaluated more rigorously in Phase 3.

Phase 3: Testing is on a much larger number of patients. The aims are to evaluate the efficacy of a drug more rigorously and to provide more information on its toxicity. Phase 3 trials need to be randomised clinical trials to meet FDA requirements, and at least one of the randomised clinical trials usually needs to be conducted in the US. Typically 500 to 3000 patients are exposed to a drug during this phase of drug development.

Phase 4: Post Marketing Surveillance

Phase 4 trials are held after a drug has been approved for marketing. The main reasons to do this phase study are to find out more about the side effects and safety of the drug. Long term risk and benefits will be clarified. How well the drug works when it is used widely will then be shown.

1.8.3.3 Management of adverse events during clinical trials

Good clinical practice requires the investigator to report to the sponsor any serious adverse events occurring during clinical trials with a new drug, but does not usually concern the management of these events. At the beginning of a clinical trial, little is known of the clinical tolerance of a new product, and when abnormalities appear the investigator must routinely consider the possibility that they have been caused by the drug. The first volunteers and patients to whom the drug is administered are therefore closely monitored. They have agreed to participate in a trial, but the benefit they hope to gain, in comparison with available treatments, has obviously not yet been demonstrated. Therefore, for the different parties engaged in clinical trials, it is essential to have the means of rapid detection of an abnormality and an assessment of the product's role. This

explains the repetition of clinical and laboratory examinations in the trial protocols: the examinations must be frequent and the results of the laboratory tests analysed from day to day. When hospitalised patients are involved, intensified monitoring is feasible, giving the investigator time to gather arguments for or against the continuation of treatment (Adams et al., 1991).

The principal questions are:

- Has the product caused the abnormality?

  A drug-related origin must be accepted if sufficient evidence cannot be found for another satisfactory explanation: either a complication of the treated disease or another concomitant disease.

- Is the likelihood of the abnormality enhanced by personal characteristics of the patient?

  The patient may have metabolic or kinetic characteristics that would explain or induce this abnormality, although the product could be well tolerated by other patients.

- Should administration of the product to the patient be interrupted?

  In principle this should be considered every time that the role of the drug in the appearance of a potentially serious abnormality cannot be eliminated.

In order to manage ADRs, pharmaceutical companies provide a brochure (known as the investigator brochure) containing guidelines for the management of clinical or laboratory abnormalities occurring during clinical trials.

1.8.3.4 Continuum of risk and benefit assessment for pharmacovigilance

Adverse events have to be known and health care professionals have to measure the risk and the benefit of drugs to aid their decision-making. Patients must be protected from experiencing unnecessary adverse events. Every country has laws to protect public health and this is becoming managed globally. Regulatory compliance is required. As a result, companies gain by succeeding in the surveillance and thus succeed in maintaining a positive reputation.

In order to assess an ADR the following should be considered:

- The primary disease involved
- A full description of full manifestation
- The timing of the adverse reaction in relation to the onset of therapy
- Relation to dose or dose interval
- Reversibility on cessation of drug
- Laboratory data: biochemical
- Characteristics of the population at risk such as age and sex of those affected.
- Detailed medical history which will supply important information on the likelihood of a patient experiencing an ADR and on the assessment of causality.

1.8.3.5 Role of a typical drug safety department

The drug safety department of pharmaceutical companies collects, investigates and reports serious spontaneous event data in a prompt and efficient manner, and identifies signals of events for further assessment. Members of the department also study signals and assess risks involved.

In a drug safety department, reports are made for submission to the authorities based on the information listed below. Also, there is a narrative in the report which focuses on relevant factual information, including specified patients' data (i.e. lab data and reporters' comments on relatedness). Irrelevant discussion should not be included.

1.8.3.6 List of data

- Identifiable patient i.e. initials, age, gender. Age is an important element in assessing the event as some conditions are more prevalent in certain populations, i.e. elderly or paediatric patients. Also in certain age groups patients are more susceptible.
- Reporter: the person who reports the fact.
- Medical history: focus on relevant history, previous occurrence of the same or a similar condition, pre-existing conditions, previous medical, surgical or radiotherapy treatments.
- Medication information: suspected drug, concomitant medications, dosage (interval and cumulative), dosage form, route of administration, indication for use.
- Event: The original reporter's terms should be used to describe the event. Diagnosis, syndromes, signs or symptoms and primary events are coded using standard vocabulary.

- Event of death: circumstances at time of death, pre-terminal events, event contributing to death, result of autopsy.
- Time course of treatment and event: onset of event, start and stop date of treatment, course of event if treatment was discontinued or dose reduced, dechallenge or rechallenge
- Relationship of event to dosage
- Outcome of event: recovered, improved, persisting, recovered with sequelae, outcome death, fatal (only used if the death is possibly related to the event), unknown.
- Lab tests: tests used to diagnose or confirm the event, to exclude alternative diagnoses, to rule out alternative aetiologies. Both positive and negative tests should be reported.
- Follow-up: further information to answer standard questions about events or missing factors.

Several groups of physicians have examined "global introspection" as a method for diagnosis. When having a set of different cases diagnosed by several different experts they have found that the level of disagreement is very high. These formal methods have included defined criteria, algorithms and visual analogue scales (Stephens, 1991).

1.8.3.7 Method of causality assessment

There are many different methods.

The Naranjo method is widely used to assess causality between drugs and adverse events. This method asks 10 questions (see below). The answers are "yes", "no", or "unknown". The total score is categorised as "less than 1", "2-4", "5-7" or" more than 8", and the assessment of the drug/event relationship for the adverse event is "unlikely", "possible", "probable" or "definite" respectively. The advantage of using this method will be elaborated (Medical Assessment & Case review of single cases. Roche, 2003).

The questions asked are:

1) Are there previous conclusive reports on this reaction?
2) Did the adverse event occurr after the suspected drug was administered?
3) Did the adverse reaction appear when the drug was discontinued, or a specific antagonist was administered?
4) Did the adverse reaction reappear when the drug was readministered?
5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?
6) Did the reaction disappear when a placebo was given?
7) Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?
8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?
9) Did the patient have a similar reaction to the same or a similar drug in any previous exposure?
10) Was the adverse event confirmed by any objective evidence?

1.8.3.8 Factors to be considered in causality assessment:

- Confirmed by rechallenge
- Confirmed by Lab data
- Known characteristic of drug or class plausibility
- Treatment information
- Plausible time course, treatment at event onset, reaction immediately following administration (within 3 minutes).
- Similar cases

Other potential causes are underlying disease, other concurrent or historic conditions and concomitant treatments.

Most drug companies use an algorithm such as Naranjo or global introspection. An algorithm can be defined in this context as a formalised process.
The pharmaceutical industry makes serious demands on all methods of diagnosis.

- It must be sensitive and specific. If it is not sensitive it will be accused of bias by its critics, but at the same time it is important not to raise problems unnecessarily.
- It must be able to use every bit of information available. The industry usually has both the time and staff to acquire further information and occasionally hospital records are made available.
- It must balance the possibilities of drug cause and non-drug cause for each factor.

European ABO classification

Category A:

Reports including good reason and sufficient documentation to assume a causal relationship (plausible, conceivable, likely but not necessarily highly probable).

Category B:

Reports containing information which accepts the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may be doubtful.

Category O:

Reports where causality is, for one reason or another, not assessable.

e.g. missing or conflicting data.

(ADR & Pharmacovigilance Roche, 2002)

1.8.3.9 Limitations of causality assessment

- Difficulty in proving connection between drug and event
- Inability to quantify contribution of causality
- Difficulty in assessing case over a period of time
- Causality assessment initially, but later abandoned

1.9 Risk management

Risk management is an important procedure for any pharmaceutical company. All drugs have to be monitored throughout their life cycle. The importance of risk management will be made clear through the example of tolcapone.

Risk-identifying and signal detection methods used by companies are:

- Pre-clinical and clinical data
- Case assessment and analysis of similar events
- Review of medical literature, use of health care data e.g. Cochlane Library
- Specially designed epidemiological studies

Most companies conduct a phase 4 observational study to further evaluate the drug safety, in terms of the relative risk in comparison with other pre-existing therapies.

It is important to:

Identify issues and put them into context

Assess risks and benefits

Identify and analyse options

Select a strategy

Implement strategy

Evaluate results

1.10 Evidence based medicine (EBM)

Evidence based clinical medicine is used to decide what treatment is most beneficial for the patient. Sackett et al. (1997) state that, "Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights and preferences in making clinical decisions about their care". Prof. Li Wan Po. (1996) states that evidence based pharmacotherapy can be defined as ensuring that patients receive the most cost effective pharmacotherapy using the best available evidence. That is to say, the information necessary for adequate decision making is the best available evidence we have so far which answers all our questions. This evidence depends on how much we know about the research, how much we understand the matter and what information is correct. Information is generally found in reports or papers which have been published after the subjects have been researched. Information has to be collected and ordered and its quality assessed. Evidence must be extracted, reviewed, integrated and combined. Different evidence can be compared if all the studies are conducted in the same way. This process is called a systematic review and the part which involves statistical analysis is called meta-analysis. A systematic review is expected to be objective and accurate in reviewing the evidence which has been obtained up to that point. To do a systematic review, it is important to decide which studies should be selected. The following items have to be borne in mind.

1) Clarification of the basis of study selection (quality of study, study design and size of study).
2) In order to avoid publication bias, consideration of the best way to search for papers thoroughly.

3) Selection of indicators such as odds ratio (OR), relative risk (RR), risk difference (RD) to show efficacy or risk size.

4) Examination to determine if the selected studies can be pooled.

5) Selection of a method for performing statistical analysis.

Sacket et al. (1997) and Li Wan Po (1996) describe the approach to EBM as follows.

1 Make questions clear:

Decide what information is most needed, for example how to select patients, interventions (treatment etc) or comparators and also what outcome is to be focussed on (efficacy or mortality etc).

2 Define outcome measures:

Defining the outcome measures to be used is a difficult task. It is important to assess the impact on patients' quality of life (QOL) rather than the immediate effects, which could be less tangible, when defining the outcome measure for chronic disease (Li Wan Po, 1996).

3 Track down relevant information:

Look for evidence which gives answers. This is usually found from clinical trials or research evidence or other sources. It is important to know which database (Medline etc), and which keywords have been used. Medline is the US National Library of Medicine's bibliographic database covering fields of medicine from more than 4,000 biomedical journals published world wide. Many organizations offer access to this database including the US National Library itself, in its PubMed service which includes over 15 million citations from Medline.

4 Critically appraise the information, check the evidence is adequate and assess its validity.

It is imperative to make sure that:

All of the important results have been included and considered, the patients' inclusion criteria are adequate and the results are clinically meaningful. Also the study design and statistical method of analysis must be assessed.

5 Apply the results of this appraisal in clinical practice.

One way of looking at the results is if the patient died or is still alive;

i) compare 2 groups (control and treatment groups) for the incident rate of death.

ii) consider the difference in the ratio of the control and treatment groups.

Another way is to look at the clinical lab values (i.e. blood pressure)

i) mean or median in the control and treatment groups.

ii) difference of the value at the mean or median

Consider the importance of the results

i) the upper limit and the lower limit of the confidence interval (a wider confidence interval means it is less reliable).

ii) the number of patients you need to treat to prevent one bad outcome (NNT) may answer the question of how many patients may have beneficial results to prevent events.

6 interpret the results and evaluate the usefulness of the study.

The best available evidence in clinical medicine is summarised by a systematic review where the results are clearly presented.

1.10.1 Narrative Review Articles and Systematic Review Articles

A narrative review tends to ignore the study design, sample size and size of data so it misses out subtle data. The data appears consistent but it does not show clearly some of the features of the study which might be important. The number of studies also tends to be selected according to the author's preference. It is most likely that the review is the author's opinion based on his or her experience. Experimental reports are also meaningful but these experimental data are not randomised, but biased. While a narrative review has these disadvantages, a systematic review is much more reliable. Following the steps shown below, clinically suitable trials can be identified and groups with and without the intervention of the study drug can be compared. The outcomes such as changes in health status owing to the drug can be evaluated, and the effect of the drug assessed. Subjects can be evaluated objectively based on current research without bias when interpreting the findings.

Steps taken for a systematic review:

Step 1: Framing questions

Step 2: Identifying relevant literature

Step 3: Assessing the quality of the literature

Step 4: Summarizing the evidence

Step 5: Interpreting the findings

1.10.2 Meta-analysis

Individual studies may be too small to show the exact effects of a drug and therefore meta-analysis can improve the reliability of the data by combining several studies. When data are pooled, every parameter such as study design, period of assessment, and inclusion/exclusion criteria of patients has to be considered and all the parameters must be the same. In the present study, all the relevant parameters are the same in those studies which are pooled and meta-analysed.

The effect measures for meta-analysis are associated with binary outcomes, risk and probability measures. This probability is called "odds" in systematic review. Risk is the possibility of harm being caused by a drug. This can be shown by risk ratio or relative risk (RR). How much less likely patients are to have a specific event when they are given a particular drug is shown by the difference between the event rates in the group taking the drug and in the placebo group, and is called absolute risk reduction (ARR) or risk difference (RD). The number needed to treat to prevent one bad outcome (NTT) can be obtained by the reciprocal of ARR/RD. This answers the question of how many patients need to be treated with the active drug to prevent a specific event. Odd ratios (OR) are used to show statistically the advantages over the relative risks. If the odds are greater than one, the event is more likely to happen than not (Hutchinson, 1997).

Khan K et al. (2002) define RR, ARR, NTT and OR as shown below:

"*Relative risk* (RR) (risk ratio): An effect measure for binary data. It is the ratio of the risk in the experimental group to the risk in the control group.

Absolute risk reduction (ARR) or *Risk difference* (RD): An effect measure for binary data. In a comparative study this is the difference in events rate between two groups. The inverse of ARR or RD produces NNT.

Number needed to treat (NNT): An effect measure for binary data. This is the number of patients who need to be treated to prevent one undesirable outcome. This is a clinically intuitive measure of the impact of a treatment.

Odds ratio (OR): An effect measure for binary data. It is the ratio of odds of an event or outcome in the experimental group to the odds of an outcome in the control group. An OR of 1.0 indicates no difference between comparison groups. For undesirable outcomes an OR that is less than 1.0 indicates that the intervention is effective in reducing the odds of that outcome."

Figure 1.7 shows calculations of OR, RR, RD and NTT calculated by the 2 x 2 table.

Figure 1.7 Calculation of OR, RR, RD and NTT from a 2 x 2 table (Adapted from Systematic Reviews BMJ 2001)

The results of a clinical trial can be displayed as a 2 x 2 table:

	Event	No event	Total
Intervention	a	b	$n_1 = a+b$
Control	c	d	$n_2 = c+d$

where a, b, c, and d are the numbers of participants with each outcome in each group. The following summary statistics can be calculated:

Odds ratio = odds of event in intervention group/ odds of event in control group
= a/b / c/d = ad/bc

Relative risk = risk of event in intervention group/ risk of event in control group
= a/(a+b) / c/(c+d)

Risk difference = risk of event in intervention group – risk of event in control group
= a / a+b – c / c+d

Number needed to treat (NNT) = 1 / risk difference
= 1 / |a/(a+b)-c(c+d)|*

*The vertical bars in the denominator of the number needed to treat formula are directions to take the absolute (positive) value. Numbers needed to treat cannot be negative, but it is important to be aware of whether the NNT is a number needed to treat for one person to benefit, or a number needed to treat for one person to be harmed.

1.10.3 Typical statistical models

There are two models called the fixed-effects model and the random-effects model. The fixed-effects model hypothesises differences and random data from the studies and happens by chance. This method is known as the Peto method. However, this method can over simplify the facts.

The random-effects model thinks individual studies vary. So by this method, the standard error is bigger and the confidential interval becomes wider.

1.11 Objectives

When deciding on drug therapy we need to be able to balance likely therapeutic efficacy (benefit) against potential harmful effects (risk). Such risk-benefit assessments are undertaken by drug companies, regulatory authorities, physicians and patients. For assessments to be made appropriately we need to have good estimates of both efficacy and adverse effects. Randomised controlled trials are often designed and powered to provide estimates of beneficial effects but harmful events are often hidden. At the time of licensing therefore, unless there are frequent adverse effects, the risk profile of therapeutic drugs is usually poorly defined. For this we need post-marketing safety studies.

The main objectives of this study are therefore to:

- examine the value of pharmacovigilance in the evaluation of a new drug, through the study of tolcapone.
- examine systematic reviews of the effectiveness and safety of tolcapone at the time when it was approved
- carry out meta-analysis of the efficacy and safety of tolcapone.

CHAPTER 2

Methods

2.1 Search strategy for identification of studies

Reports of randomised controlled trials of tolcapone were identified through a systematic search consisting of :

1. an electronic search of PubMed (http://www.ncbi.nlm.nih.gov/), and the Science Citation Index.
2. searches of the reference lists of original reports and review articles, retrieved through the electronic searches.
3. information obtained from the Roche intranet service and the Basel Library (BLIS).

2.1.1 Mind map

In order to develop and maximize ideas, the mind map method was used. Mind mapping allows expansion and exploration of an idea. This method was developed by Tony Buzan. "Risk and benefit assessment of new drug" was written in the middle of large blank sheet of paper. Main branches connected to the central image were added, radiating outwards. Each branch represented a sub-heading, key idea or aspect of the main topic. Sub-themes were added to the ends of the main branches. These added another level of detailed related ideas or sub-categories. Figure 2.1 shows an illustration of the mind map.

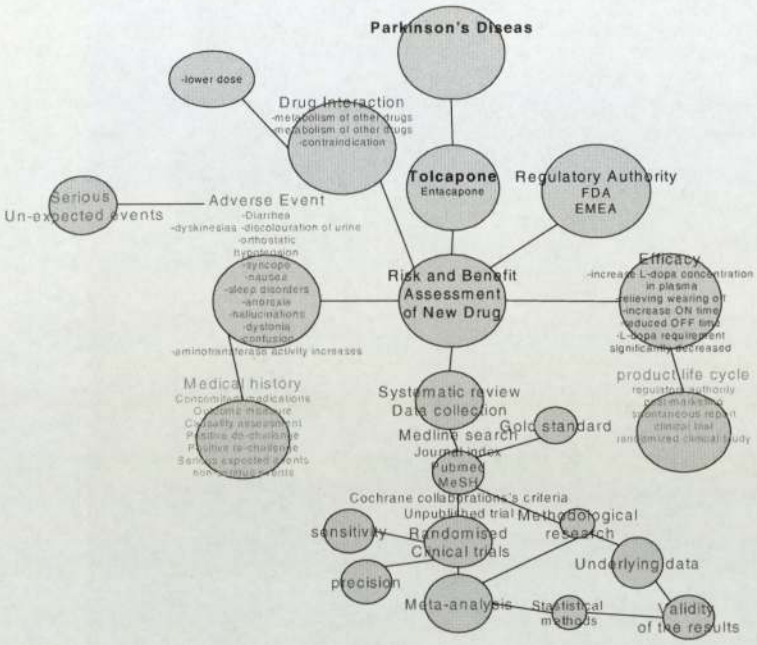


Figure 2.1. Mind map illustration

2.1.2 Search period and keywords

The computerised searches covered the period from 1990 to 2003. The terms used in the PubMed search included combinations of:

1) tolcapone; 2) Parkinson's disease, 3) benserazide or carbidopa, 4) randomised controlled trials; 5) hepatotoxicity, 6) review. Key word or title word searching was undertaken in the Science Citation Index (PubMed).

2.2 Details of search methods

1) using the key words, e.g."tolcapone / hepatotoxicity", "tolcapone" / "benserazide" or "carbidopa", "tolcapone / review", "tolcapone / parkinson's disease".
2) phrases from titles, e.g. "Tolcapone", "Parkinson's disease", the names of authors of literature articles and tolcapone, eg. "Muller T and tolcapone"; the names of journals and tolcapone, e.g. "Movement Disorder and tolcapone", "Journal of Neurology and tolcapone".
3) Using author's names e.g. "Jorga K", "Nutt JG".

2.3 Result of systematic search

One hundred and eighty two articles on tolcapone were identified through the systematic review (from 1990 to 2003). Thirty two articles were then identified with the key words "tolcapone and benseraside" and forty two articles were identified with the key words "tolcapone and carbidopa".

2.3.1 Inclusion and exclusion criteria

For a study to be included in the systematic overview, it had to be a randomised controlled trial. In order to meta-analyse, parallel studies were chosen. Patients with fluctuating PD were included. Abstracts and short reports were discarded because they provide insufficient information for pooling.

All randomised controlled trials (RCTs) published comparing tolcapone with either a placebo or an active comparator in patients with Parkinson's disease were included. Studies that did not measure clinical evidence of UPDRS or "on/off" time were excluded (studies were included if one of these was measured).

All studies had to meet the following criteria to be considered eligible for this present study:

*Randomised, double-blind trials.

*Mean patient's age more than 60.

*Mean disease duration more than 8 years.

*Mean duration of L-dopa treatment more than 7 years

*Baseline patient's characteristic measured by clinical efficacy.

The above inclusion and exclusion criteria were decided by considering the characteristics of tolcapone which is used as an adjunct therapy to L-dopa, and studies which measured clinical evidence were included, as binary data was required for meta-analysis.

2.3.2 Study selection

When a thorough electronic search is undertaken many relevant studies can be missed because of poor indexing. For this reason, it is recommended that electronic searching is supplemented by manual searching, by reviewing reference lists of articles retrieved and writing to appropriate investigators known to have a keen interest in the drug involved.

In the present study, Myllyla's study was not picked up by electronic search but from the references from retrieved literature.

2.3.3 Data Extraction

Quantitative data were extracted and safety data relating to the frequency and type of adverse events was assessed for the identified trials. Other important information, such as the patient characteristics in each trial and descriptive methodologies, was also extracted.

2.3.4 Outcome measures

In order to assess risk and benefit, the outcome measures of the 5 studies finally selected were adverse events and clinical efficacy as listed below:

1. "On / off" time changes between the baseline and weeks 6 – 12.
2. Changes in L-dopa doses (mg or dose form)
3. United Parkinson's Disease Rating Scale (UPDRS) score I, II, III or total (which score or scores measured varied depending on the studies)

*not all studies measured everything

*efficacy was evaluated using patients' self-rating diaries and investigators' global assessments (IGA)

*UPDRS score description is given in Appendix 3

2.3.5 Data conversion

In order to convert standard deviation (SD) into standard error of the mean (SEM), the following formula was used:

$SEM=SD/\sqrt{n}$

Dealing with missing data:

Some of the studies did not provide SD or SEM.

In one study (Kurth et al. 1997), neither SD nor SEM were reported for all the items in the placebo group, apart from "change in L-dopa dose". The UPDRS score changes from the baseline were read from the graph, therefore no SD or SEM was given. In one study (Rajput et al. 1997), neither SD or SEM were reported for "off" time for any of the groups, the average of SD of the study of Baas et al. (1997) was used.

Calculation of standard error of the mean of change:

The following formula was used:

$SEM= \sqrt{[SD_1^2 /n_1+SD_2^2/n_2]}$

SD_1 is the SD at baseline

n_1 is the sample size at baseline

SD_2 is SD at end of treatment

n_2 is the sample size at end of treatment

CHAPTER 3

The efficacy and adverse events of tolcapone in the treatment of patients with Parkinson's disease

3.1 Introduction and objective

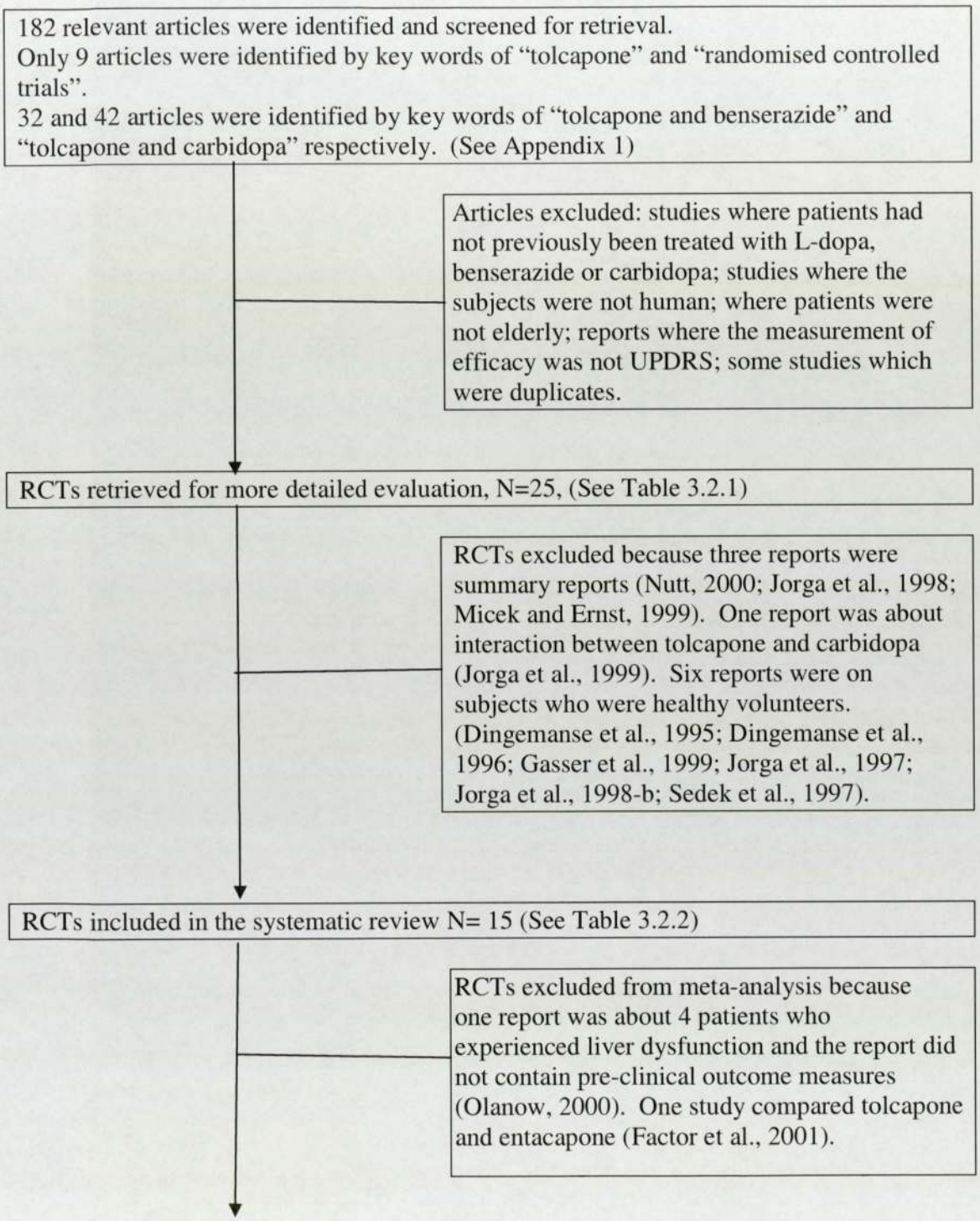
Medical therapy with tolcapone aims to decrease the dose of L-dopa given to patients but to increase its efficacy so that the patient's unpleasant adverse events related to L-dopa are reduced. The adverse events of tolcapone include nausea, vomiting and dyskinesia. The objective described in this chapter is to systematically review the evidence for the efficacy and safety of tolcapone.

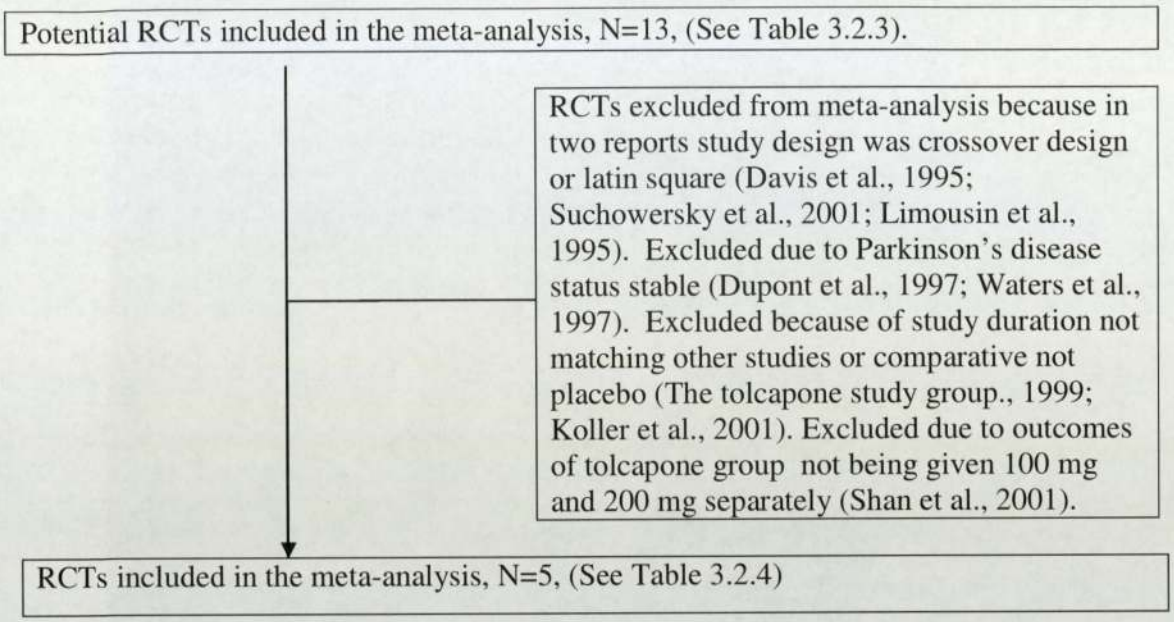
3.2 Results of systematic search

One hundred and eighty two articles on tolcapone (from 1990 to 2003) were identified through the systematic review . A list of all potentially relevant RCTs are listed in Appendix 1. Thirty two articles (references) were then identified with keywords of "tolcapone and benseraside" and forty two articles were identified with keywords of "tolcapone and carbidopa". Patients with fluctuating PD were included and analysed separately depending on the duration of the studies (6 weeks or 12 weeks).
The process by which the studies were selected is shown in Figure 3.1.

Figure 3.1

Flow chart of the criteria and process of inclusion of studies in the systematic review





* Dupont 1997, study design is crossover between tolcapone doses, but not crossover between tolcapone and placebo.

Table 3.2.1: RCTs retrieved for more detailed evaluation, N=25

Adler et al., 1998; Baas et al., 1997; Dingemanse et al., 1995; Dingemanse et al., 1996; Davis et al., 1995; Dupont et al., 1997; Factor et al., 2001; Gasser et al., 1999; Jorga et al., 1997; Jorga et al., 1998-a; Jorga et al., 1998-b; Jorga et al., 1999; Koller et al., 2001; Kurth et al., 1997; Limousin et al., 1995; Micek et al., 1999; Nutt et al., 2000; Olanow et al., 2000; Rajput et al., 1997; Sedek et al., 1997; Shan et al., 2001; Shchowersky et al., 2001; The tolcapone study group 1999; Waters et al., 1997; Myllyla et al., 1997

Table 3.2.2: RCTs included in the systematic review N= 15

Adler et al., 1998; Baas et al., 1997; Davis et al., 1995; Dupont et al., 1997; Factor et al., 2001; Koller et al., 2001; Kurth et al., 1997; Limousin et al., 1995; Olanow et al., 2000; Rajput et al., 1997; Shan et al., 2001; Shchowersky et al., 2001; The tolcapone study group 1999; Waters et al., 1997; Myllyla et al., 1997

Table 3.2.3: Potential RCTs included in the meta-analysis, N=13,

Adler et al., 1998; Baas et al., 1997; Davis et al., 1995; Dupont et al., 1997; Koller et al., 2001; Kurth et al., 1997; Limousin et al., 1995; Rajput et al., 1997; Shan et al., 2001; Shchowersky et al., 2001; The tolcapone study group 1999; Waters et al., 1997; Myllyla et al., 1997

Table 3.2.4: RCTs included in the meta-analysis, N=5,

Study duration 6 weeks: Adler et al., 1998; Kurth et al., 1997; Myllyla et al., 1997
Study duration 12 weeks: Baas et al., 1997; Rajput et al., 1997

3.3 Characteristics of RCTs

Only a few studies were identified after being screened according to certain inclusion and exclusion criteria. A list of all potentially relevant articles are listed in Appendix 1-1. Five RCTs met the inclusion criteria of double blind, randomised, parallel placebo controlled studies. Three out of the five studies gave results at 6 weeks and two gave results at 12 weeks. The characteristics of each trial are described in Table 3.3.1.

Table 3.3.1 Summary of characteristics of trials included in meta-analysis

Trial	Design	Dose/Frequency	Location	Duration	No. of PT	No.of PT Withdrawal due to AE	Sex	Mean age	PD severity
Adler et al. (1998)	DB Parallel	100mg TID 200mg TID	U.S.A & Canada	6 weeks	Total: 215 Placebo: 72 100mg:69 200mg:74	Total: 12 Placebo 5 100mg: 2 200mg: 3	 M/F: 52:20 M/F: 46:23 M/F 51:23	 64±8 62±12 61±10	Fluctuating
Baas et al. (1997)	DB Parallel	100mg TID 200mg TID	Europe	12 weeks	Total: 177 Placebo: 58 100mg: 60 200mg: 59	Total: 27 Placebo.: 4 100mg: 14 200mg: 9	 M/F: 35:23 M/F: 31:29 M/F: 33:26	 64±8 62±10 63±9	Fluctuating
Kurth et al. (1997)	DB Parallel	50mg TID 200mg TID 400mg TID	U.S.A	6 weeks	Total: 161 Placebo: 42 50mg: 41 200mg: 40 400mg: 38	Total: 10	 M/F: 28:14 M/F: 25:16 M/F: 26:14 M/F: 26:12	 64±9 63±11 65±8 66±8	Fluctuating
Myllyla et al. (1997)	DB Parallel	50mg TID 200mg TID 400mg TID	Europe & Australia	6 weeks	Total: 154 (133) Placebo: 42 (37) 50mg: 37 (34) 200mg: 38 (31) 400mg: 37 (31)	Total: 10 Placebo: 3 50 mg: 2 200mg: 1 400mg: 3	 M/F: 24:18 M/F: 23:14 M/F: 24:14 M/F: 24:13	 63±9 62±9 62±11 63±9	Fluctuating
Rajput et al. (1997)	DB Parallel	100mg TID 200mg TID	U.S.A & Canada	12 weeks	Total: 202 Placebo: 66 100mg: 69 200mg: 67	Total 37 Placebo: 10 100 mg: 12 200 mg: 15	 M/F: 47:19 M/F: 40:29 M/F: 52:15	 65±10 63±9 64±9	Fluctuating

Abbreviations: DB: double blind; 50mg, 100 mg, 200 mg, 400 mg indicate doses of tolcapone; M: male, F: female; TID: 3 times daily, PT: patient, AE: adverse event

Myllyla et al. (1997): The numbers of patients who were evaluated for the outcomes of efficacy are in brackets.

3.4 The Efficacy of tolcapone in the treatment of PD

The efficacy and safety of the study drug were assessed between the baseline and week 6 (Adler et al., 1998, Kurth et al., 1997, Myllyla et al., 1997) or week 12 (Baas et al., 1997, Rajput et al., 1997). A summary of the efficacy is shown in Table 3.4.1. Table 3.4.2 shows the results + standard deviation (SD). The patients were examined by the same investigator at all the visits and at the same time of day as with the baseline examination. The primary efficacy measure was a change from the baseline in "on/off" time recorded in the patient's diaries. The trials used doses ranging from 50 mg to 400 mg. Two trials (Kurth et al., 1997 and Myllyla et al., 1997) used 50 mg, 200 mg and 400 mg. The other trials used 100 mg and 200 mg. Overall, 200 mg seemed to be the most effective dose although there were some differences between the studies and the dose groups in each parameter. With some studies a higher dose gave a good result but with others it did not. Both trials which assessed at 12 weeks (Baas et al., 1997, Rajput et al., 1997) used the same doses of 100 mg and 200 mg. With regard to "on" time and "off" time, Rajput et al., (1997) did not provide a standard error for the placebo results. For meta-analysis of the weighted mean difference, the average of standard errors of Baas's study was used.

Table 3.4.1 Summary of efficacy: data where change from baseline (data are shown ± SEM)

Duration	Study	Intervention/ dose	"On" time (hour)	"Off" time (hour)	Change in L-dopa dose (mg)	Change in L-dopa dose (number of pills)	UPDRS I	UPDRS II	UPDRS III	UPDRS Total
6 weeks	Adler et al. (1998)	Placebo	0.30±0.30	-0.30±0.30	-0.50±20.10	0.00±0.10	n/a	-0.7±0.4	-1.2±0.7	-2.2±0.9
		100 mg	2.10±0.30	-2.00±0.30	-185.50±20.60	-0.50±0.10	n/a	-0.4±0.4	-2.3±0.7	-2.9±0.9
		200 mg	2.30±0.30	-2.50±0.30	-251.50±19.90	-1.20±0.10	n/a	-0.5±0.4	-2.4±0.7	-2.9±0.9
	Kurth et al. (1997)	Placebo	-0.12±0.28	-0.04±0.27	-31.20±29.40	0.00±0.20	n/a	n/a	0±n/a	n/a
		50 mg	1.69±0.29	-1.66±0.27	-139.00±31.00	-0.30±0.20	n/a	n/a	-5.0±n/a	n/a
		200 mg	1.63±0.26	-1.61±0.28	-200.00±31.00	-0.90±0.20	n/a	n/a	-4.0±n/a	n/a
		400 mg	1.60±0.32	-1.81±0.30	-175.00±34.00	-0.70±0.20	n/a	n/a	-3.0±n/a	n/a
	Myllyla et al. (1997)	Placebo	-0.34±0.51	-0.11±0.43	2.40±18.00	n/a	0.0±0.2	-0.8±0.5	-0.3±1.7	n/a
		50 mg	1.65±0.56	-0.94±0.48	-56.00±19.80	n/a	-0.3±0.2	-0.6±0.5	-2.6±1.9	n/a
		200 mg	2.08±0.58	-1.78±0.50	-79.10±19.90	n/a	0.0±0.2	-1.4±0.5	-5.8±1.9	n/a
		400 mg	1.42±0.59	-1.15±0.51	-13.30±20.20	n/a	-0.5±0.2	-1.5±0.5	-3.7±2.0	n/a
12 weeks	Baas et al. (1997)	Placebo	-0.11±0.45	-0.67±0.37	-28.90±26.20	n/a	n/a	n/a	-2.1±1.1	n/a
		100 mg	1.73±0.42	-2.03±0.34	-108.90±23.40	n/a	n/a	n/a	-4.2±1.0	n/a
		200 mg	1.73±0.42	-1.57±0.34	-122.20±23.90	n/a	n/a	n/a	-6.5±1.0	n/a
	Rajput et al. (1997)	Placebo	n/a	-1.40±n/a	n/a	-0.10±0.10	0.0±0.2	-0.3±0.5	-0.4±0.9	-0.7±1.2
		100 mg	n/a	-2.30±n/a	n/a	-0.60±0.10	0.3±0.2	-0.8±0.4	-1.9±0.9	-2.4±1.1
		200 mg	n/a	-3.20±n/a	n/a	-0.70±0.10	0.2±0.2	0.2±0.4	-2.0±0.9	-1.7±1.2

*Kurth's results are from the investigator evaluation (waking day = 10 hours)

Table 3.4.2 Summary of efficacy: data where change from baseline (data are shown ± SD)

Duration	Study	Intervention/ dose	"On" time (hour)	"Off" time (hour)	Change in L-dopa dose (mg)
6 weeks	Adler et al. (1998)	Placebo	0.30±2.55	-0.30±2.46	-0.50±170.55
		100 mg	2.10±2.49	-2.00±2.49	-185.50±171.12
		200 mg	2.30±2.58	-2.50±2.58	-251.50±171.19
	Kurth et al. (1997)	Placebo	-0.12±1.81	-0.04±1.75	-31.20±190.53
		50 mg	1.69±1.86	-1.66±1.73	-139.00±198.50
		200 mg	1.63±1.64	-1.61±1.77	-200.00±196.06
		400 mg	1.60±1.97	-1.81±1.85	-175.00±209.59
	Myllyla et al. (1997)	Placebo	-0.34±3.11	-0.11±2.63	2.40±116.65
		50 mg	1.65±3.27	-0.94±2.80	-56.00±120.44
		200 mg	2.08±3.21	-1.78±2.76	-79.10±122.67
		400 mg	1.42±3.30	-1.15±2.85	-13.30±122.87
12 weeks	Baas et al. (1997)	Placebo	-0.11±3.43	-0.67±2.82	-28.90±199.53
		100 mg	1.73±3.25	-2.03±2.63	-108.90±181.26
		200 mg	1.73±6.23	-1.57±2.61	-122.20±183.58
	Rajput et al. (1997)	Placebo	n/a	-1.40±2.69	n/a
		100 mg	n/a	-2.30±2.69	n/a
		200 mg	n/a	-3.20±2.69	n/a

*Kurth's results are from the investigator evaluation (waking day = 10 hours)
*SD of Rajput "off" time is average of Baas's study.

"Off" time was measured in all 5 studies (Adler et al., 1998; Kurth et al., 1997; Myllyla et al., 1997; Baas et al., 1997; Rajput et al., 1997). All the studies considered the waking time to be 16 hours, apart from that of Kurth et al. (1997), who considered the waking time to be 10 hours. Figure 3.3 shows the investigator evaluation of "on" time "off" time in the study of Kurth et al.

If the results were given as percentages they were converted into hours. The percentage of "off" time in 2 studies (Baas et al., 1997; Myllyla et al., 1997) was the percentage of 16 hours. The percentage of "off" time in the study of Kurth et al. (1997) was the percentage of 10 hours. All the studies except the study of Kurth et al., (1997) assessed the response at 6 weeks and showed that 200 mg was the most effective dose. Kurth et al. (1997) showed similar results for all of the tolcapone doses (50 mg, 200 mg 400 mg) but 400 mg was the most effective in terms of "off" time. There was an approximately 2.5 hours reduction in "off" time from the baseline. With the studies assessed at 12 weeks, Baas et al. (1997) reported that the patients' "off" time was reduced by 2.03 hours with 100 mg, which is more than with 200 mg (minus 1.57 hours), but Rajput et al. (1997) reported that the patients' "off" time was reduced by 3.2 hours with 200 mg but minus 2.3 hours with 100 mg. All of the studies showed a fairly similar reduction of "off" time both at the 6 week assessment and at the 12 week assessment. (Figure 3.2)

"On" time was measured in all three trials with a 6 week assessment, and in 1 trial (Baas et al., 1997) with a 12 week assessment. Most of the studies showed that 200 mg tolcapone was the most effective. The Figure 3.2 shows all tolcapone dose groups had an improved "on-off" time compared with the placebo groups.

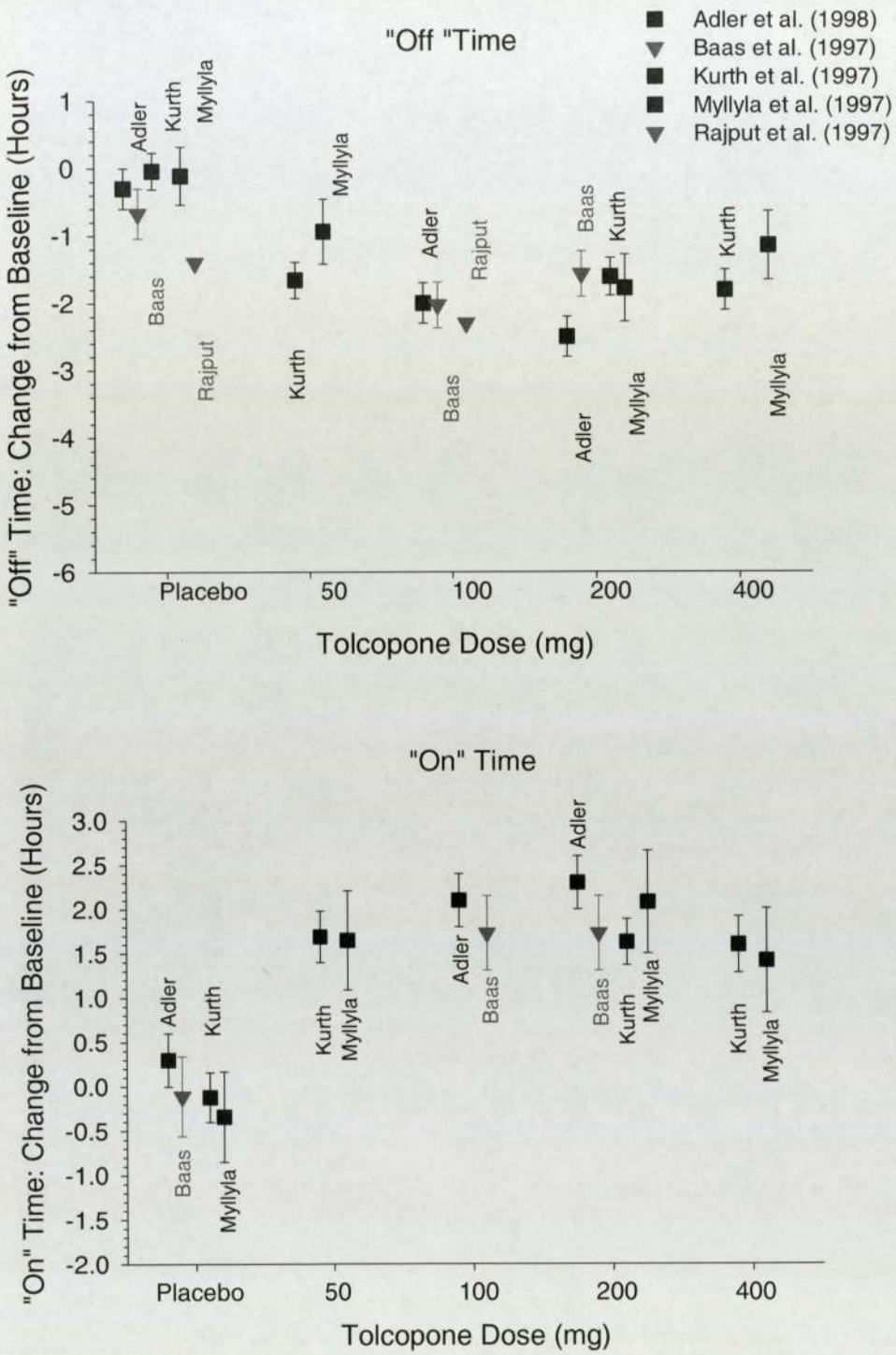


Figure 3.2 Changes from the baseline of "off" time and "on" time
Only the first author is listed in the graph
■ studies assessed at 6 weeks
▼ studies assessed at 12 weeks

The study of Kurth et al. (1997) showed that 50 mg was the most effective in terms of "on" time, but the results were similar for each dose, as well as for the "off" time results. The study of Baas et al. (1997) showed that the results of 100 mg tolcapone and 200 mg tolcapone were the same. As with "on-off" time, waking time was considered to be 16 hours except in the study of Kurth et al. (1997). Two studies (Baas et al., 1997, Myllyla et al., 1997) reported "on" time as a percentage, and this was converted into hours, as a percentage of 16 hours. Kurth et al. (1997) reported the investigator's evaluation of "on" time and "off" time over a 10 hour day, and the patients' diary evaluation of "on" time and "off" time assumed a 16 hour waking time. The patients' diary evaluation did not provide a standard error with the results at the baseline or at 6 weeks. Therefore, the investigator assessment was used for the analysis.

The results of the investigator's evaluations of "on" time and "off" time (Kurth et al., 1997) are shown in Figure 3.3. This clearly shows a significant reduction of "off" time and an increase in total "on" time.

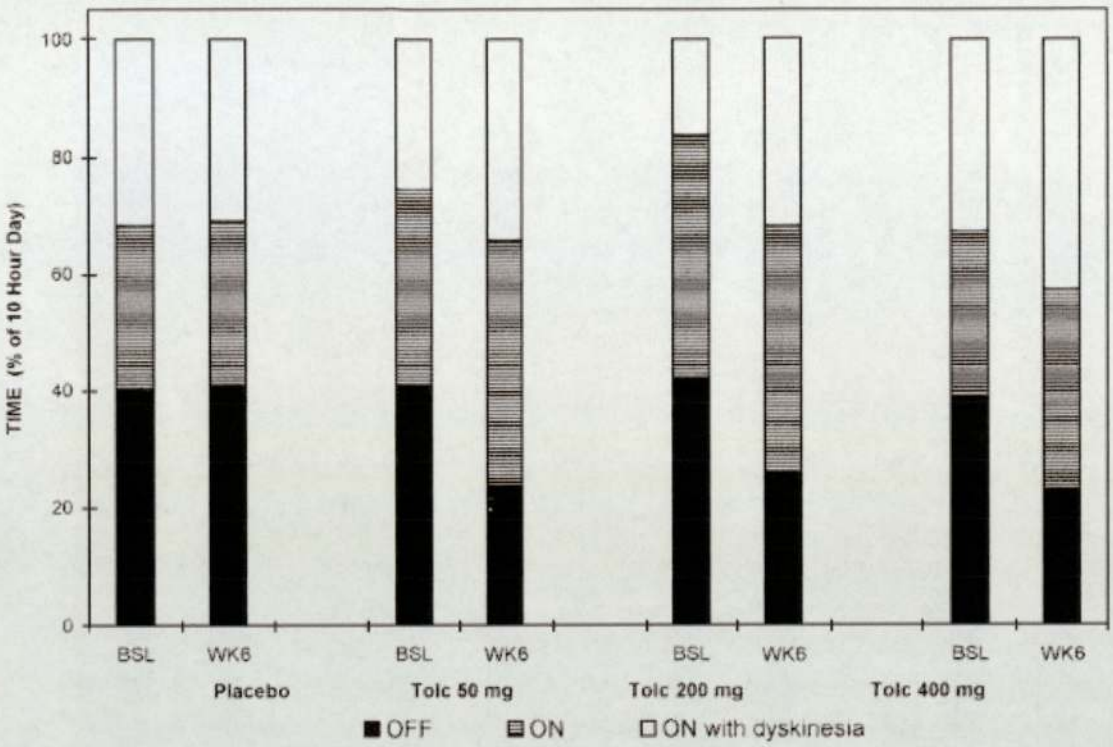


Figure 3.3 The investigator evaluation of "on" time and "off" time (Adapted from Kurth et al., 1997; 48; 81 - 87)
Mean "off," "on," and "on" with dyskinesia times at baseline (BL) and week 6 (WK6) as a percentage of the investigator-assessed 10-hour day. Patients were examined at 30-minute intervals for 10 hours (8 AM to 6 PM) and scored as "off," "on," or "on" with dyskinesia. The percentage of time in each of these categories was then calculated for the baseline (BL) and week 6 (WK6) 10-hour days. There was a statistically significant reduction in "off" time and increase in total "on" time ("on" and "on" with dyskinesia) for all three tolcapone doses, with no change in the placebo group.

Where there was a change in the L-dopa dose, a significant reduction was shown in all the studies. Figure 3.4 shows changes in the L-dopa dose in four of the studies. All of the studies reported their results in mg, except Rajput et al. (1997) who reported the results in dose form of L-dopa. Two studies (Adler et al., 1998, Kurth et al., 1997) reported in both mg and the number of intakes of L-dopa pills. All of the studies reported that there was a significant difference from the placebo.

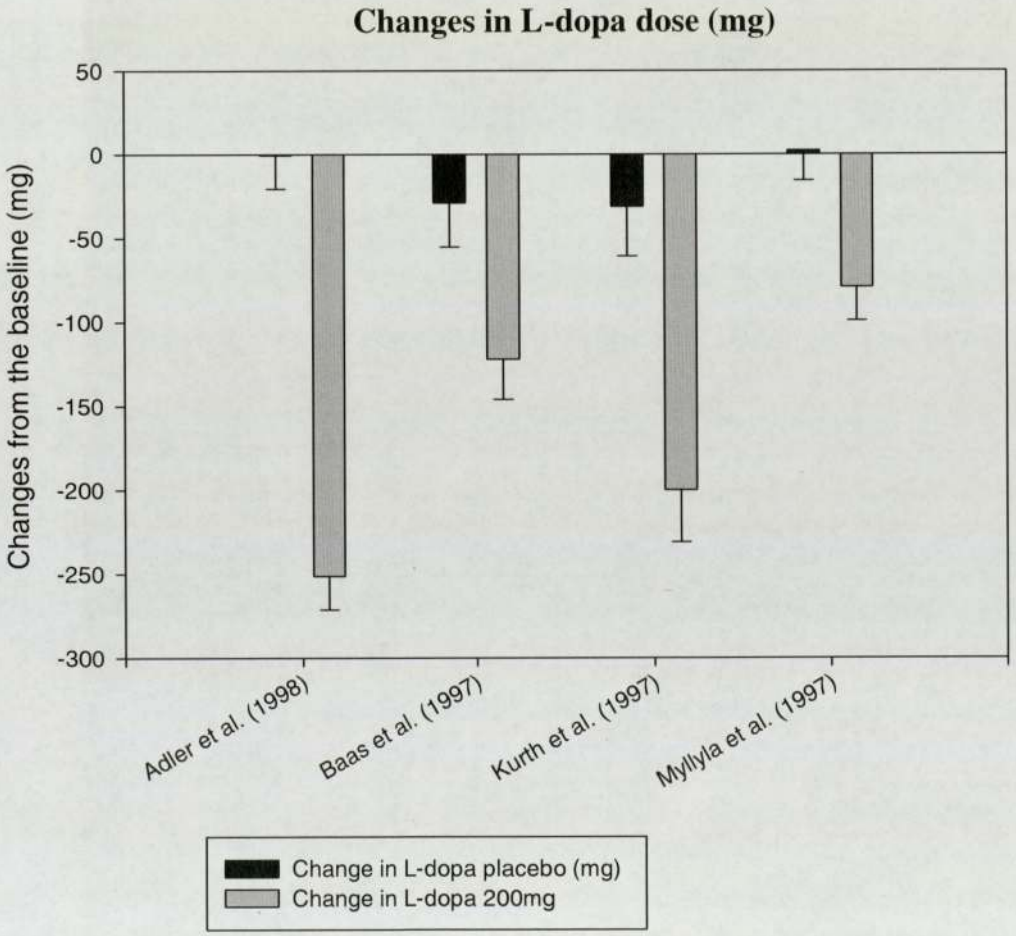


Figure 3.4 Changes in L-dopa dose (mg)
Adler et al. (1998), Kurth et al. (1997) and Myllyla et al. (1997) assessed at 6 weeks.
Baas et al. (1997) assessed at 12 weeks

For the UPDRS score, the activities of daily living UPDRS III (motor subscale) were assessed in all of the studies. Figure 3.5 shows UPDRS III score changes from the baseline. Where there is simply a comparison of the results, all of the studies showed that the UPDRS III score of all the tolcapone dose groups improved compared with the placebo group. However, all of the studies apart from Baas et al. (1997) stated that there was no significant difference between the tolcapone and placebo groups. Baas et al. (1997) reported that the score for UPDRS III was reduced significantly between the baseline and week 12 in the 200 mg tolcapone group although it was not significant in the 100 mg tolcapone group.

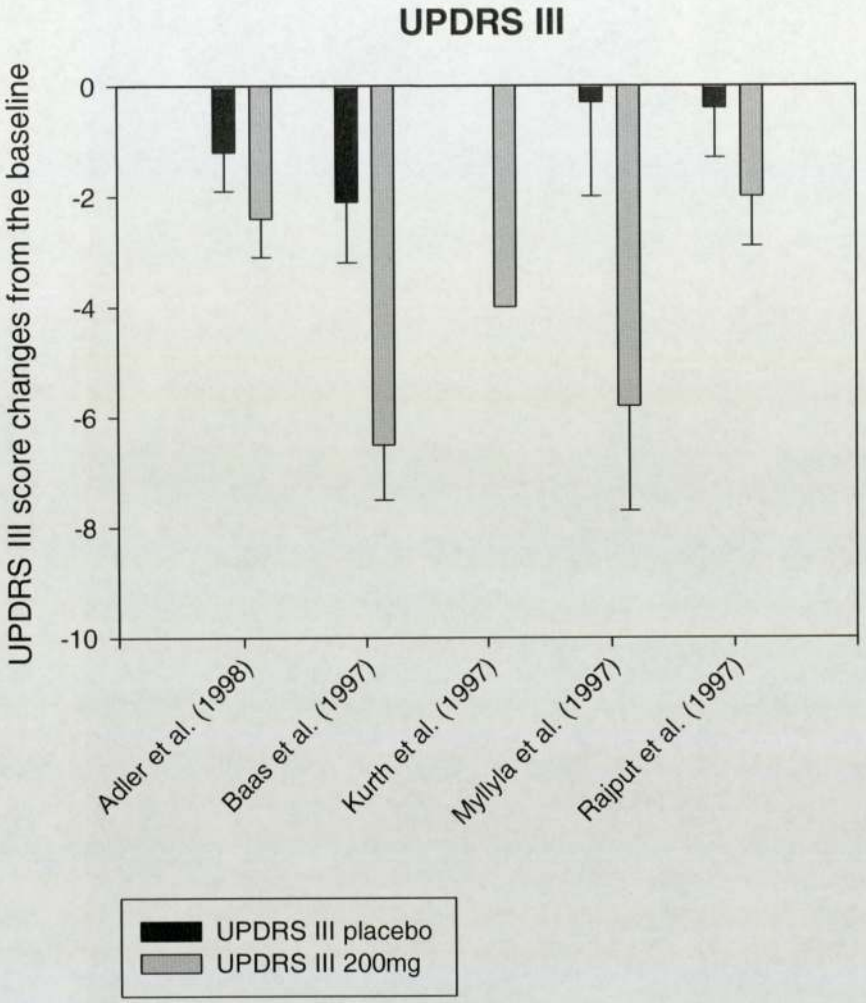


Figure 3.5 UPDRS III score changes from the baseline
Adler et al. (1998), Kurth et al. (1997) and Myllyla et al. (1997) assessed at 6 weeks.
Baas et al. (1997) and Rajput et al. (1997) assessed at 12 weeks

3.5 Adverse Events

3.5.1 Tolerability

An integrated summary table for adverse events is shown in Table 3.5.1.1. The majority of the high incidence adverse events were dopaminergic events such as dyskinesia, nausea, vomiting, dizziness, postural hypertension and psychiatric symptoms including amnesia, agitation, confusion and hallucinations. These dopaminergic events are already known as they have been reported with L-dopa therapy without COMT inhibition. The most commonly occurring non-dopaminergic side effects with tolcapone are believed to be diarrhoea and urine discolouration. These appeared in the trials which evaluated outcomes at 12 weeks but diarrhoea was not reported in any trials assessed at 6 weeks. The pooled rate ratio suggests that patients who received tolcapone are more likely to have dopaminergic adverse events. Other events more often seen in the studies are confusion (at 6 weeks), dystonia (at 6 weeks), sleep disorder (at 12 weeks), somnolence (at 12 weeks) and excessive dreaming (both at 6 weeks and at 12 weeks). Dizziness was reported in studies assessed at 6 weeks but was not reported in the studies assessed at 12 weeks.

Anorexia and sleep disorder are said to be the most commonly observed adverse events associated with the use of tolcapone, occurring more frequently than in placebo-treated patients (www.fda.gov). Sleep disorder was reported in half of the studies (Myllyla et al., 1997, Baas et al., 1997 and Rajput et al., 1997) and anorexia was reported in only 2 studies (Adler et al., 1998 and Rajput et al., 1997). The number of patients who experienced sleep disorder was considerable in every study which reported the event of

sleep disorder, but was still not significant compared to the placebo group. Both sleep disorder and anorexia can be a common adverse reaction to all drugs, and it is therefore, conceivable that they were not reported in some studies.

Table 3.5.1.1 Summary of the common adverse events in randomised controlled trials of tolcapone

Adverse event	Study duration / total number of patients / number of patients with event			
	6 weeks (Adler et al., 1998; Kurth et al., 1997: Myllyla et al., 1997)		12 weeks (Baas et al., 1997; Rajput et al., 1997)	
	Placebo group (total n=176) Adler et al. (1998): 72 Kurth et al. (1997): 42 Myllyla et al. (1997): 42	Tolcapone group (total n=394) Adler et al. (1998): 143 Kurth et al. (1997): 119 Myllyla et al. (1997): 112	Placebo group (total n=124) Baas et al. (1997): 58 Rajput et al. (1997): 66	Tolcapone group (total n=255) Baas et al. (1997): 119 Rajput et al. (1997): 136
Nervous disorder				
Dyskinesia	30	195	24	131
Sleep disorder	0	3	25	71
Hallucination	4	21	7	22
Excessive dreaming	7	24	8	19
Dizziness	5	27	0	0
Confusion	9	23	0	0
Dystonia	18	42	0	0
Agitation	1	3	0	0
Restlessness	0	0	0	7
Headache	0	0	0	8
Tremor	0	0	0	0
Gastrointestinal disorder				
Nausea	14	92	24	79
Diarrhoea	0	0	11	46
Anorexia	4	27	10	31
Vomiting	0	15	2	12
Xerostomia	3	11	1	13

Table 3.5.1.1 Summary of the common adverse events in randomised controlled trials of tolcapone (Cont.)

Adverse event	Study duration / total number of patients / number of patients with event			
	6 weeks (Adler et al., 1998; Kurth et al., 1997: Myllyla et al., 1997)		12 weeks (Baas et al., 1997; Rajput et al., 1997)	
	Placebo group (total n=176) Adler et al. (1998): 72 Kurth et al. (1997): 42 Myllyla et al. (1997): 42	Tolcapone group (total n=394) Adler et al. (1998): 143 Kurth et al. (1997): 119 Myllyla et al. (1997): 112	Placebo group (total n=124) Baas et al. (1997): 58 Rajput et al. (1997): 66	Tolcapone group (total n=255) Baas et al. (1997): 119 Rajput et al. (1997): 136
Gastrointestinal disorder (conti.)				
Constipation	0	5	4	16
Abdominal pain	0	0	1	5
Dyspnoea	0	0	0	0
Urinary disorder				
Urine discolouration	1	18	0	10
Musculo-skeletal				
Muscle cramp	1	13	6	23
Othostatic complaints	0	0	6	28
Cardiovascular disorder				
Hypotension	4	12	0	5
Respiratory disorder				
Upper respiratory tract infection	1	2	3	14
Dyspnoea	0	0	1	4

Table 3.5.1.1 Summary of the common adverse events in randomised controlled trials of tolcapone (Cont.)

Adverse event	Study duration / total number of patients / number of patients with event			
	6 weeks (Adler et al., 1998; Kurth et al., 1997: Myllyla et al., 1997)		12 weeks (Baas et al., 1997; Rajput et al., 1997)	
	Placebo group (total n=176) Adler et al. (1998): 72 Kurth et al. (1997): 42 Myllyla et al. (1997): 42	Tolcapone group (total n=394) Adler et al. (1998): 143 Kurth et al. (1997): 119 Myllyla et al. (1997): 112	Placebo group (total n=124) Baas et al. (1997): 58 Rajput et al. (1997): 66	Tolcapone group (total n=255) Baas et al. (1997): 119 Rajput et al. (1997): 136
Endocrine disorder				
Increased sweating	2	13	0	0
Psychiatric disorder				
Depression	0	4	0	0
Other				
Falling	0	0	3	15

3.5.2 Liver function test

No detailed liver function test results were reported in any of the studies. However, 4 cases led to "black box" warning and more intensive monitoring in the United States, as shown in Figure 3.6. Kurth et al. (1997), Adler et al. (1998) and Myllyla et al. (1997) indicated there were no changes in liver function test during their studies. Baas et al. (1997) reported that mean concentration of aspartate amino-transferase (AST) and alanine amino-transferase (ALT) were higher at week 6 than with placebo. Marked ALT concentrations were found 1 patient in the 100 mg tolcapone group and 2 patients in the 200 mg tolcapone group. One of these patients was withdrawn from the study on day 113. Similarly, Rajput et al. (1997) reported that tolcapone treatment was associated with raised AST and ALT concentrations in 3 patients in the 100 mg tolcapone group and 2 patients in the 200 mg tolcapone group. One patient in the 200 mg group was withdrawn as a result of these liver function changes. This patient's values were three to five times the upper limit of the normal range but the patient remained asymptomatic (Rajput et al., 1997).

3.5.2.1 Case report

One case report (patient 1 in Figure 3.6) was identified through a literature search using "case report" and "tolcapone" as key words. Spahr et al. (2000) reported the following case which is one of the four which are described by Olanow et al. (2000). This case is also described by Spahr et al. (2000) and Assal et al. (1998).

Outline of clinical course:

A 74 year old female patient was admitted to hospital on 3 June 1998 for acute hepatitis. The patient's medical history included Parkinson's disease which she had suffered for more than 15 years. The patient was initially treated with L-dopa (100 mg) / benserazide (25 mg) three times a day with a good sustained response. Amantadine 100 mg twice a day was added several years later for better neurological control. Other medical history included mild orthostatic hypotension and recurrent limb oedema. There was no history of pre-existing liver disease. Nine weeks before admission, amatadine was discontinued and tolcapone 100 mg twice daily was started to improve motor functions. One week before hospitalisation, the patient became jaundiced, and was diagnosed with grade 2 hepatic encephalopathy. Tolcapone and all other medications were discontinued. The patient's condition gradually deteriotated. On day 8, her ALT levels progressively decreased to 1783 IU / L but were not measured thereafter. The patient went into a hepatic coma and died on 17 June 1998, thirteen days after hospitalisation. The pathology and biochemistry results were as follows: prothrombin time 21 sec, bilirubin level 367 μmol/L (normal: 5 – 17 μmol/L), alkaline phosphatase 177 IU/L (normal: 30 – 125 IU/L), aspartate amino-transferase (AST) 2541 IU/L (normal: 11 – 32 IU/L), alanine amino-transferase (ALT) 2904 IU/L (normal: 9 – 36 IU/L), serum lactate 2.1 mmol/L (normal: 1 – 1.9 mmol/L).

This case has been considered to be fulminant hepatic failure owing to the tolcapone as there was no evidence of pre-existing liver disease.

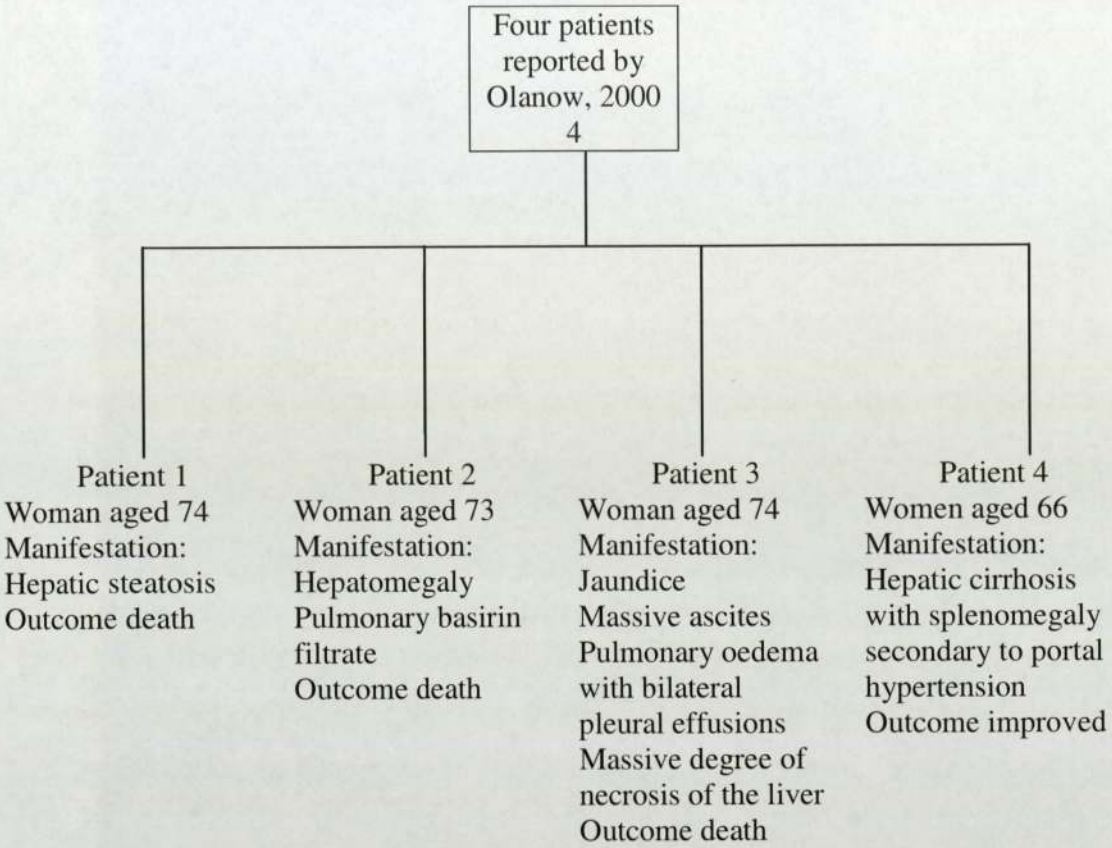


Figure 3.6
The cases led to a "black box" warning and more intensive monitoring requirements in the United States. In all these 4 cases, the patients were female and had no history of previous liver disease.

3.5.3 Withdrawal

The number of patients who were withdrawn from the studies owing to adverse events are shown in Table 3.5.3.1.

Table 3.5.3.1 The number of patients withdrawn owing to adverse events

	Study	Placebo	100 mg Tolcapone	200 mg Tolcapone
6 weeks	Adler et al. (1998)	5/72	2/69	3/74
	Myllyla et al. (1997)	3/42	n/a	1/38
12 weeks	Baas et al. (1997)	4/58	14/60	9/59
	Rajput et al. (1997)	10/66	12/69	15/67

The numbers on the right indicate the number of patients in the group. The numbers on the left indicate the number of patients withdrawn owing to adverse events.

Kurth et al. (1997) is not included because only the total number of withdrawals was reported.

3.6 Conclusion

The clinical trials included in this meta-analysis used tolcapone doses ranging from 50 mg to 400 mg. The results of the 200 mg dose were used for pooling as this dose is known to produce the best pharmacokinetic profile (Jorga et al., 1998, Sedgek et al., 1997), and every trial used this dose. All of the outcomes showed that the efficacy of tolcapone is superior to that of the placebo. In terms of length of trial, the results were not significantly different at 6 and 12 weeks.

All of the studies stated that tolcapone showed a favourable tolerability. Most adverse events reported affected the nervous system and the gastrointestinal system.
A significant difference appeared between placebo and tolcapone with diarrhoea (12 weeks) and urine discolouration (6 weeks and 12 weeks).

In general, the major adverse events were dopaminergic and were probably related to the increased L-dopa bioavailability provided by tolcapone. This suggests that tolcapone is a useful treatment for Parkinson's disease with fluctuation, used together with a decarboxylase inhibitor, benserazide or carbidopa.

CHAPTER 4

Meta-Analysis

4.1 Introduction and objectives

A systematic review allows a more objective appraisal of the evidence than a traditional narrative review (Egger et al., 2001). Given the results of a number of trials, a simple average which does not consider individual differences is not an adequate summary. A more reasonable estimate of effect can be made through meta-analysis. In Chapter 3 the clinical benefit and risk associated with the use of tolcapone were discussed in a semi-quantitative manner. In order to obtain more reliable and accurate estimates of effect, a meta-analysis has been performed on appropriate data and is described in this chapter. Differences or similarity in treatment effects were examined across the trials included.

4.2 Heterogeneity

Meta-analysis not only estimates the common effect across the trials but also portrays the differences between the studies. In order to obtain the reliability of any inferences made, a careful investigation of heterogeneity across the studies is important.

4.3 Publication bias

If all the trials carried out in the past had been published, there would be no publication bias. However, this is not realistic. The tendency is to publish trials with positive results rather than negative ones. In the first instance, a funnel plot is a good visual method to investigate this issue and is widely used to determine the dispersion of results amongst studies but this technique requires a large number of studies to be examined. If there is asymmetry in the plot, this indicates that there is a bias. If the studies use the same method and the same conditions, and measure the same things repeatedly, the values are scattered around the true value symmetrically. The larger the sample size, the smaller the deviation expected.

4.4 Results of meta-analysis of the outcomes in the studies included

The primary outcomes of "on" time, "off" time and changes in daily L-dopa dose were summarised using the method of weighted mean difference (WMD), which is called effect size meta-analysis. WMD was used because all of the studies included here measured the outcomes on the same scale or could be converted to the same scale. Statistical software (Statsdirect Version 2.4.4) was used in the present investigation. The Q statistic is given with its associated probability on the number of studies minus 1 degree of freedom, (N-1). This has low power as a strict test of homogeneity. A large value of Q (low probability of occurrence) indicates that there is significant heterogeneity between the studies. There are no comprehensive rules on when to use random effects and when to use fixed effects models (DerSimonian and Laird, 1986). In the present study, the fixed effects model was used when the Q statistic showed no significance.

4.4.1 Effect size (weighted mean difference) meta-analysis

4.4.1.1 Changes in daily L-dopa dose (mg)

Changes in the L-dopa daily dose were available in all three studies at the 6 weeks assessment but one of two studies (Rajput et al., 1997) did not measure the L-dopa dose reduction in mg at 12 weeks assessment, therefore only the 6 weeks assessment was valid for meta-analysis.

Table 4.4.1.1 shows the Forest plot of changes in the daily L-dopa dose (mg) at 6 weeks, with tolcapone vs placebo. The data (measured at 6 weeks) gives changes from the baseline. The Q statistics suggest a significant heterogeneity of the effect (Q = 17.63 with 2 df, p = 0.0001), therefore the fixed effects model was not suitable, so a random effects model was used (Figure 4.1).

Table 4.4.1.1 Tolcapone vs placebo changes in daily L-dopa dose (mg) at 6 weeks meta-analysis

Study	Patients in tolcapone 200 mg group	Patients in placebo group	Effect size (weighted mean difference)	95 % CI
Adler et al. (1998)	74	72	-251	-306.06, -195.94
Kurth et al. (1997)	40	42	-168.8	-251.42, -86.17
Myllyla et al. (1997)	31	37	-81.5	-138.13, -24.87
Pooled estimate of effect size wmd+ =			-168.90	-204.57, -133.24
Q ("non-combinability" for effect size) = 17.63 (df = 2) P = 0.0001				
DerSimonian-Laird pooled wmd =			-167.21	-276.22, -58.20

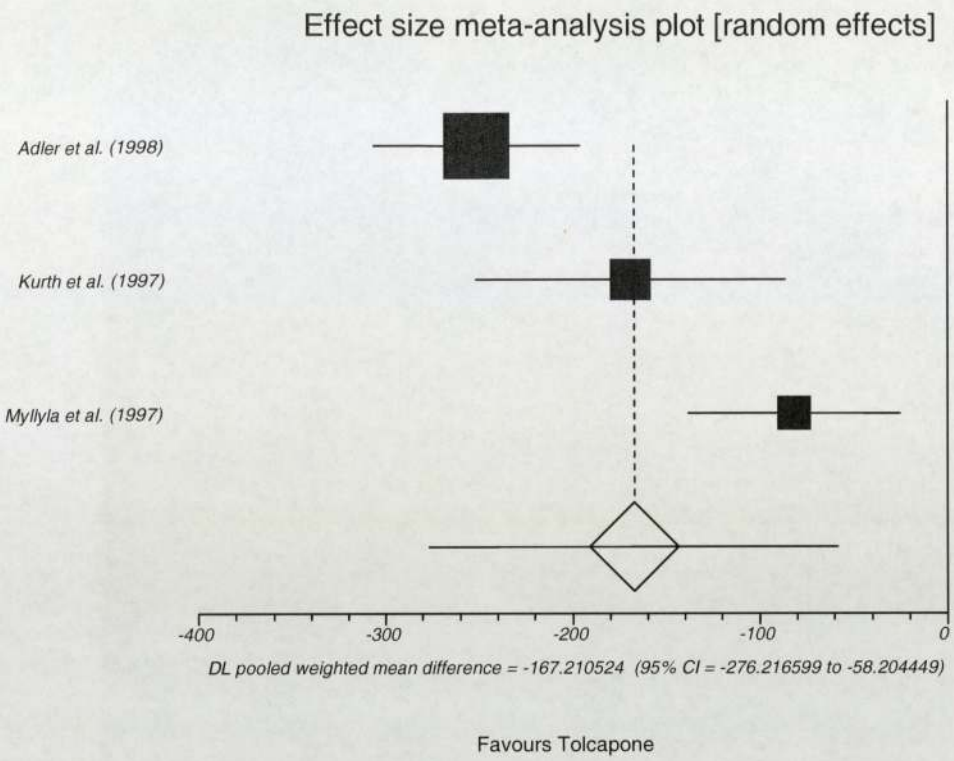


Figure 4.1 Effect size for changes in L-dopa daily dose (mg) data gives changes from the baseline, showing significant heterogeneity. Q = 17.63 with df = 2
P = 0.0001

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. It indicates that the study of Adler et al. (1998) gives the biggest sample. The pooled estimate is shown as a diamond shape. The vertical dotted line is the pooled estimate of effect. This figure shows results in favour of tolcapone.

4.4.1.2 "on" time increase (hours)

"On" time increase was available for the three studies that assessed changes in the L-dopa daily dose at 6 weeks. Only these three studies were valid for meta-analysis as one of the two studies that assessed at 12 weeks, Rajput et al. (1997), did not measure "on" time increase.

The Q statistics suggested that there was no significant difference between the studies ($Q = 0.59$ with 2 df, $p = 0.74$) (Table 4.4.1.2), therefore the fixed effects model was used. Figure 4.2 shows the Forest plot of the effect size for "on" time increase.

The data (measured at 6 weeks) gives changes from the baseline. The results falling to the right of the line of the no effect indicate the beneficial effect observed in the tolcapone groups.

Table 4.4.1.2 Tolcapone vs placebo "on" time increase at 6 weeks meta-analysis

Study	Patients in tolcapone 200 mg group	Patients in placebo group	Effect size (weighted mean difference)	95 % CI
Adler et al. (1998)	74	72	2	1.17, 2.83
Kurth et al. (1997)	40	42	1.75	1.00, 2.50
Myllyla et al. (1997)	31	37	2.38	0.87, 3.89
Pooled estimate of effect size wmd+ =			1.92	1.40, 2.44
Q ("non-combinability" for effect size) = 0.59 (df = 2) P = 0.7443				

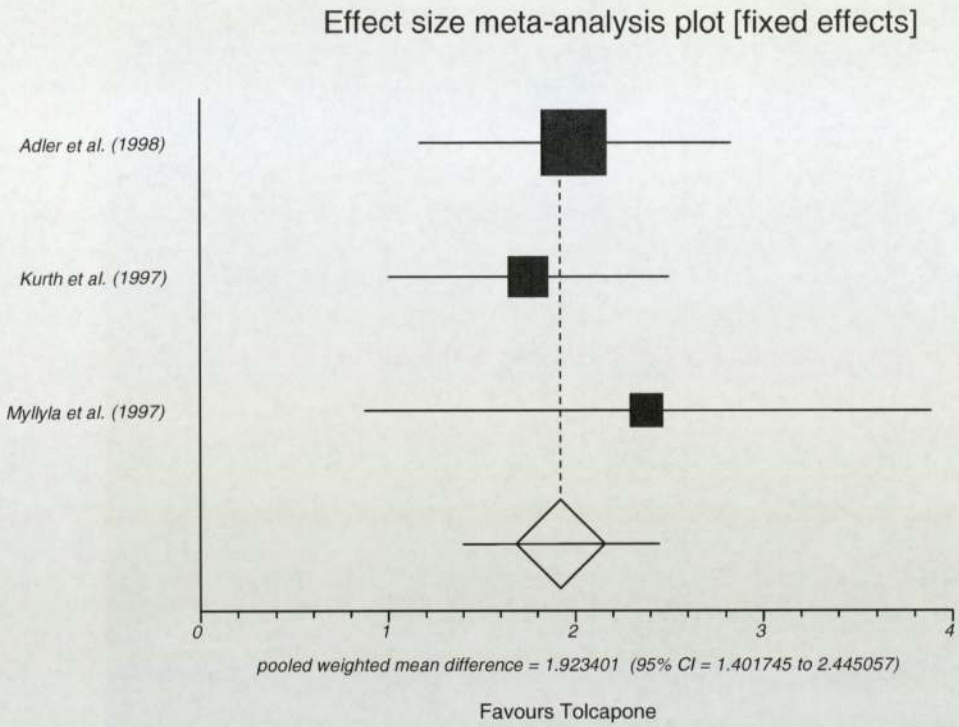


Figure 4.2 Effect size for "on" time increase data gives changes from the baseline (measured at 6 weeks), showing no significant heterogeneity. Q = 0.59 with df = 2 P = 0.7443

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. It indicates that the study of Adler et al. (1998) gives the biggest sample. The pooled estimate is shown as a diamond shape. The vertical dotted line is pooled estimate of effect. This figure shows results in favour of tolcapone.

4.4.1.3 "off" time decrease (hours)

"Off" time decrease was available for all five studies. Both the 6 weeks assessment and the 12 weeks assessment showed no significant heterogeneity between the studies. Q = 1.29 with 2 df, P = 0.5239 and Q = 1.72 with 1 df, P = 0.1894, respectively (Table 4.4.1.3 and Table 4.4.1.4). Rajput et al. (1997) did not provide standard deviation or standard error of the means. As StatDirect requires standard deviation when effect size is calculated, the average of SD of the study of Baas et al. (1997) was used.

Figure 4.3 and Figure 4.4 show the Forest plot of effect size for changes in "off" time decrease measured at 6 weeks and at 12 weeks, respectively.

The data gives changes from the baseline. The results falling to the left of the line of the no effect (one) indicate the beneficial effects observed in the tolcapone groups.

Table 4.4.1.3 Tolcapone vs placebo "off" time decrease at 6 weeks meta-analysis

Study	Patients in tolcapone 200 mg group	Patients in placebo group	Effect size (weighted mean difference)	95 % CI
Adler et al. (1998)	74	72	-2.2	-3.02, -1.38
Kurth et al. (1997)	40	42	-1.57	-2.33, -0.81
Myllyla et al. (1997)	31	37	-1.67	-2.95, -0.39
Pooled estimate of effect size wmd+ =			-1.83	-2.34, -1.32
Q ("non-combinability" for effect size) = 1.29 (df = 2) P = 0.5239				

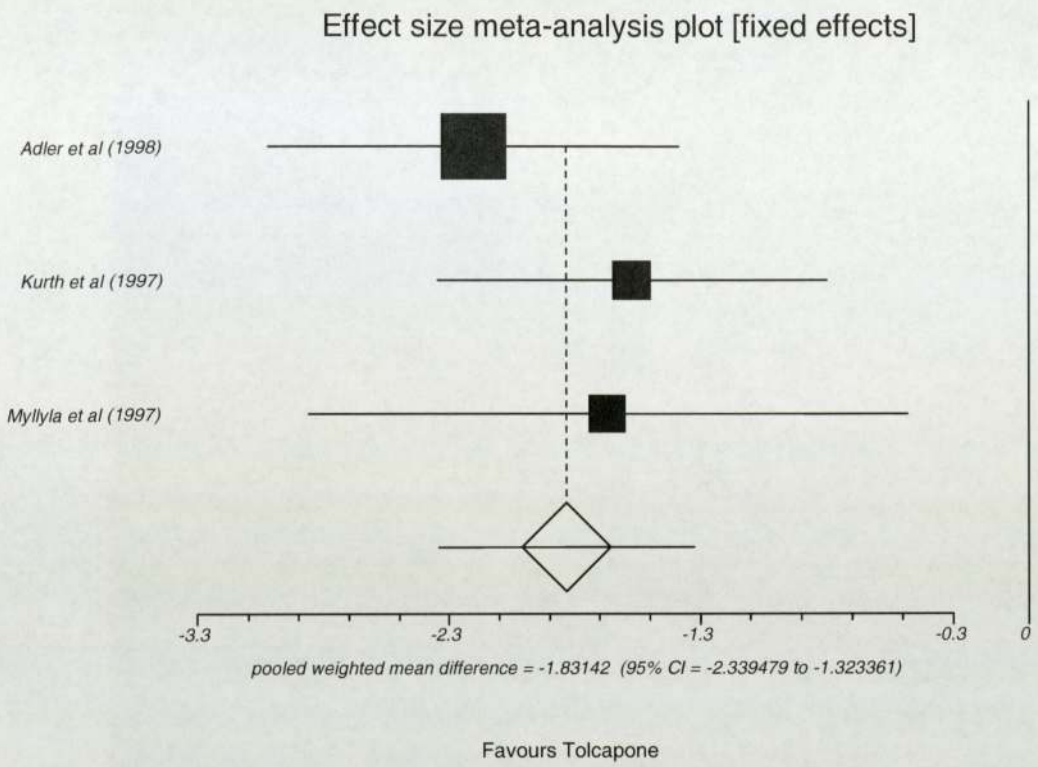


Figure 4.3 Effect size for "off" time decrease data gives changes from the baseline(measured at 6 weeks), showing no significant heterogeneity. Q = 1.29 with df = 2 P = 0.5239

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. It indicates that the study of Adler et al. (1998) gives the biggest sample. The pooled estimate is shown as a diamond shape. The vertical dotted line is the pooled estimate of effect. This figure shows results in favour of tolcapone.

Table 4.4.1.4 Tolcapone vs placebo "off" time decrease at 12 weeks meta-analysis

Study	Patients in tolcapone 200 mg group	Patients in placebo group	Effect size (weighted mean difference)	95 % CI
Baas et al. (1997)	59	58	-0.9	-1.88, 0.08
Rajput et al. (1997)	67	66	-1.8	-2.71, -0.89
Pooled estimate of effect size wmd+ =			-1.38	-2.05, -0.71
Q ("non-combinability" for effect size) = 1.72 (df = 1) P = 0.1894				

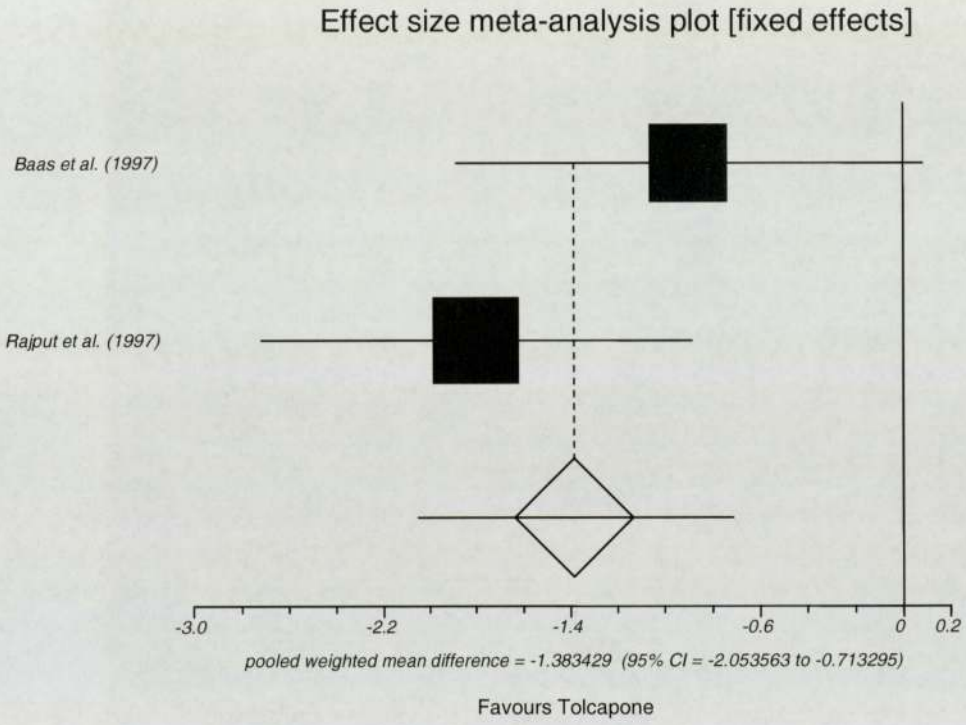


Figure 4.4 Effect size for"off" time decrease data gives changes from the baseline (measured at 12 weeks), showing no significant heterogeneity. Q = 1.72 with df = 1 P = 0.1894

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. The pooled estimate is shown as a diamond shape. The vertical dotted line is the pooled estimate of effect. This figure shows results in favour of tolcapone.

4.4.2 Withdrawal rate owing to adverse events

Figure 4.5 and Table 4.4.2.1 show the withdrawal odds ratio for tolcapone vs placebo at 6 weeks. The Forest plot shows less withdrawal in the tolcapone groups. However, more withdrawal in the tolcapone groups is shown at 12 weeks assessment (Figure 4.6 and Table 4.4.2.2).

Diarrhoea is not reported in any of studies at 6 weeks assessment, but a considerable number of patients experienced diarrhoea in the studies at 12 weeks assessment (Table 3.5.1.1). Figure 4.7 and Table 4.4.2.3 indicate that withdrawal owing to diarrhoea was more likely to occur in the tolcapone groups.

Table 4.4.2.1 Number of patients who were withdrawn due to adverse events in the 6 weeks studies

	Study	Number of patients who were withdrawn / Number of patients who received tolcapone (200 mg)	Number of patients who were withdrawn / Number of patients who received placebo	OR (95% CI)	M-H Weight
6 weeks	Adler et al. (1998)	3 / 74	5 / 72	0.57 (0.08, 3.05)	2.43
	Myllyla et al. (1997)	1 / 38	3 / 42	0.35 (0.01, 4.66)	1.39
Pooled results	Fixed effect			0.49 (0.14, 1.67)	
	Chi-square			0.74	
	"P" value			P = 0.39	
	Random effect			0.49 (0.14, 1.70)	
	Chi-square			1.25	
	Degree of freedom			1	
	"P" value			P = 0.26	

OR: Odds Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach uses DerSimonian and Laird method

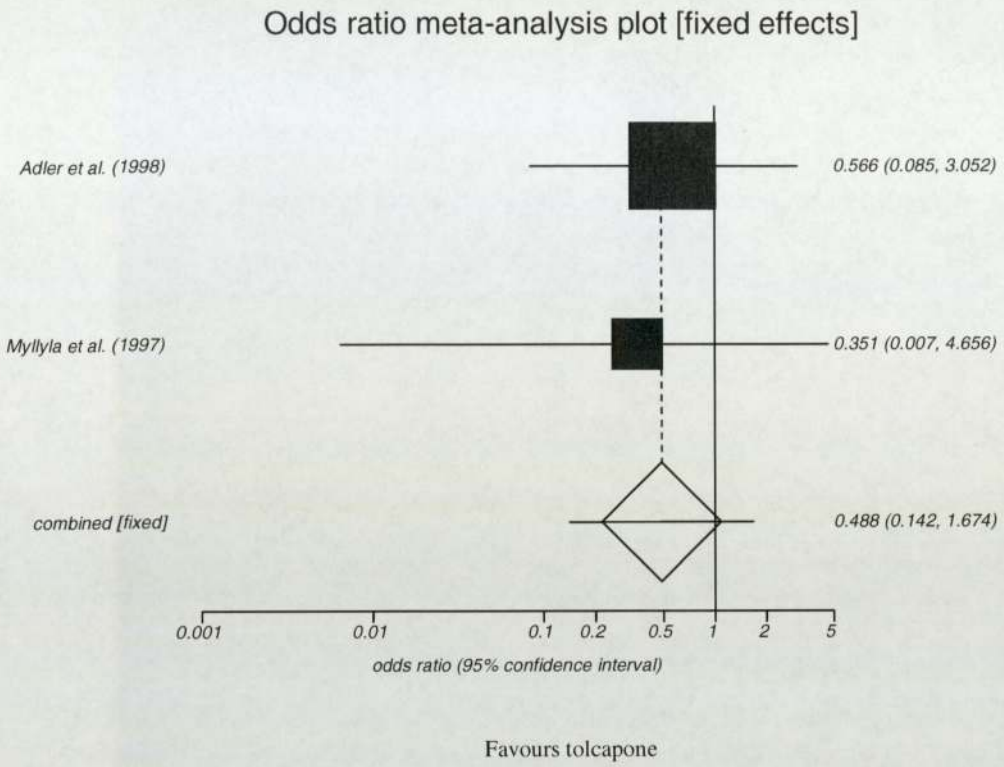


Figure 4.5 Withdrawal odds ratio for tolcapone vs placebo at 6 weeks.

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. It indicates that the study of Adler et al. (1998) gives the biggest sample size. The pooled estimate is shown as a diamond shape. The vertical dotted line is the pooled estimate of effect. The figure shows a non-significant result in favour of treatment with patients who received placebo withdrawing more often from treatment than patients who received tolcapone. Kurth et al. (1997) is not included in this figure because only the total number of withdrawals was reported but not each withdrawal number for the placebo and tolcapone groups.

Table 4.4.2.2 Number of patients who were withdrawn due to adverse events in the 12 weeks studies

	Study	Number of patients who were withdrawn / Number of patients who received tolcapone (200 mg)	Number of patients who were withdrawn / Number of patients who received placebo	OR (95% CI)	M-H Weight
12 weeks	**Baas et al. (1997)**	9 / 59	4 / 58	2.43 (0.62, 11.41)	1.71
	Rajput et al. (1997)	15 / 67	10 / 66	1.61 (0.61, 4.39)	3.91
Pooled results	**Fixed effect**			1.86 (0.91, 3.82)	
	Chi-square			2.36	
	"P" value			P = 0.12	
	Random effect			1.85 (0.90, 3.81)	
	Chi-square			2.83	
	Degree of freedom			1	
	"P" value			P = 0.09	

OR: Odds Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach use Der Simonian and Laird method

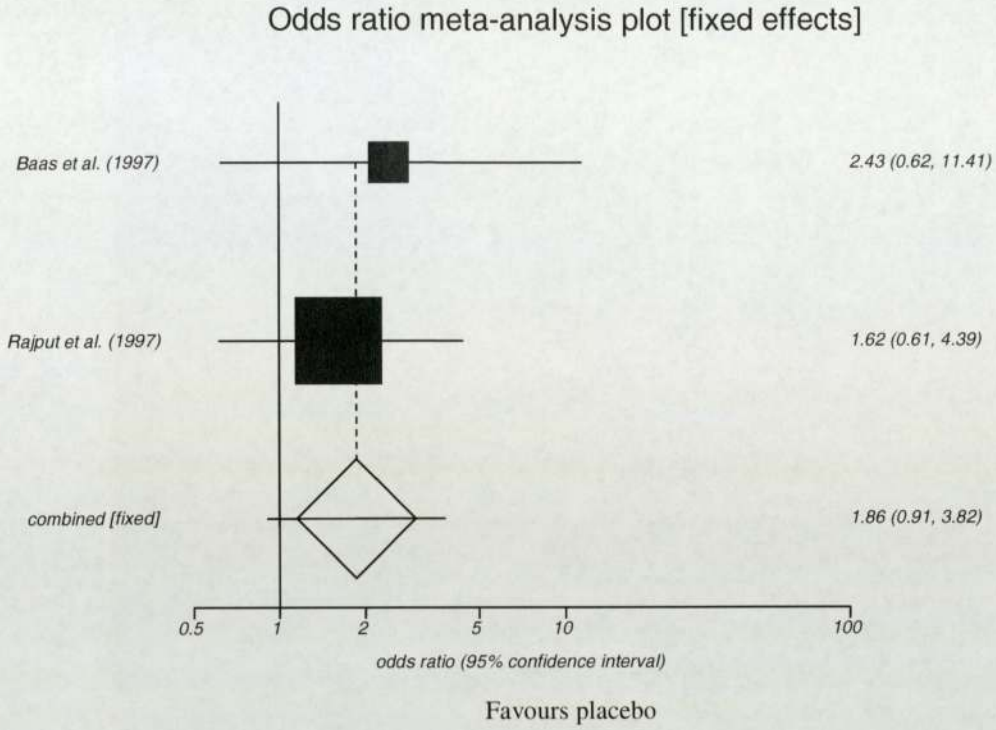


Figure 4.6 Withdrawal odds ratio for tolcapone vs placebo at 12 weeks.

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. The pooled estimate is shown as a diamond shape. The vertical dotted line is the pooled estimate of effect.
This figure shows a non-significant result in favour of placebo. More patients withdrew in the tolcapone group than in the placebo group.

Table 4.4.2.3 Number of patients who were withdrawn due to diarrhoea in the 12 weeks studies

	Study	Number of patients who were withdrawn / Number of patients who received tolcapone (100, 200 mg)	Number of patients who were withdrawn / Number of patients who received placebo	OR (95% CI)	M-H Weight
12 weeks	**Baas et al. (1997)**	10 / 119	0 / 58	11.17 (0.71, 231.78)	0.31
	Rajput et al. (1997)	8 / 136	2 / 66	1.70 (0.30, 7.96)	1.58
Pooled results	**Fixed effect**			3.24 (0.94, 11.13)	
	Chi-square			3.01	
	"P" value			P = 0.08	
	Random effect			3.00 (0.50, 17.98)	
	Chi-square			1.44	
	Degree of freedom			1	
	"P" value			P = 0.23	

OR: Odds Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach use Der Simonian and Laird method

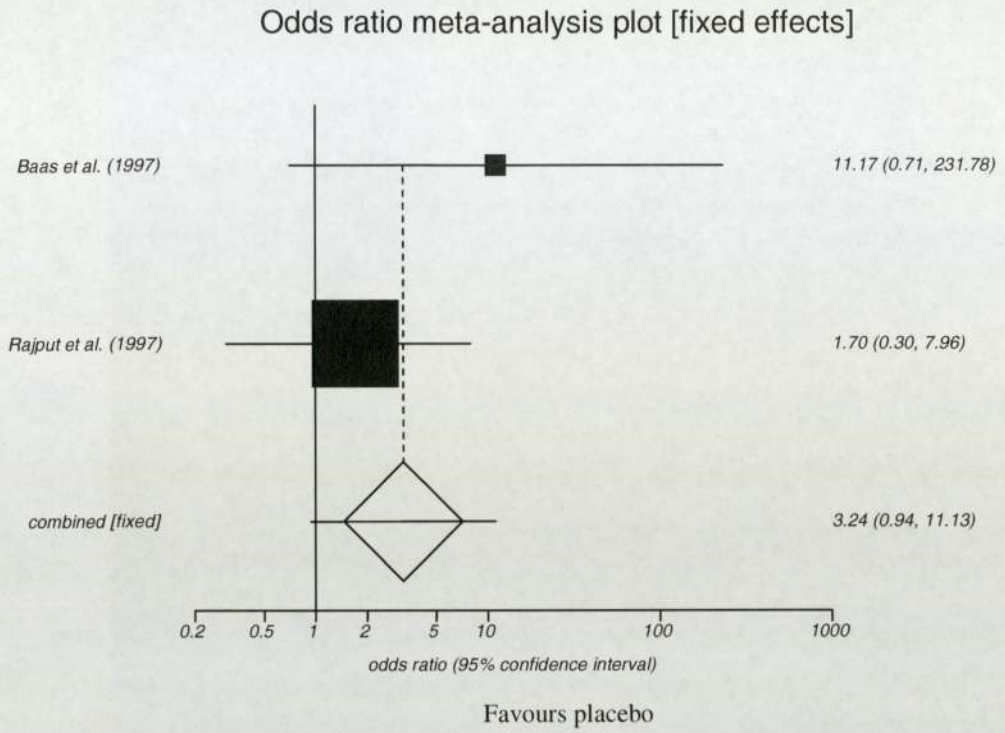


Figure 4.7 Withdrawal odds ratio due to diarrhoea for tolcapone vs placebo at 12 weeks showing more patients withdrawn in the tolcapone group.

The squares give the estimates at each point and the horizontal line across each point gives the 95 % confidence interval. The size of the square represents the weight assigned to the study. The pooled estimate is shown as a diamond shape. The vertical dotted line is the pooled estimate of effect.
This figure shows a non-significant result in favour of placebo with more patients withdrawn in the tolcapone group than in the placebo group.

4.4.3 Adverse Events

The individual adverse events which occurred significantly in the tolcapone group were analysed. The occurrence rate of dyskinesia was increased in the tolcapone groups, which showed a relative risk of 2.78 ($P < 0.0001$) in the studies at 6 weeks assessment and a relative risk of 3.03 ($P < 0.0001$) in the studies at 12 weeks assessment. Patients experienced nausea in both the tolcapone and the placebo groups but a greater number of patients experienced it in the tolcapone group. Two 6 week assessment studies reported vomiting in the tolcapone group but in the 12 week assessment study, only Baas et al. (1997) reported that two patients experienced it in the placebo group. A significant number of patients who received tolcapone experienced dizziness in the studies at 6 weeks assessment but none in the studies at 12 weeks assessment. Patients with 100 mg tolcapone experienced it more than those with 200 mg tolcapone, and slightly more patients experienced it in the placebo group than the 200 mg tolcapone group in the study of Adler et al. (1998). The pooled relative risk for this analysis was therefore very close to the line of no effect when the 200 mg tolcapone group and the placebo group were compared (Figure 4.9). Similarly, a significant number of patients experienced sleeping disorder in the studies at 12 weeks assessment but none experienced it in the studies at 6 weeks assessment. Table 4.4.3.1 and Table 4.4.3.2 show the number of patients who experienced common adverse events in the 6 weeks and the 12 weeks studies. Figure 4.8 to Figure 4.17 show the rate ratio of each adverse event in each study. A significantly greater number of patients who received tolcapone experienced urine discoloration in comparison with those who received placebo (Figure 4.16 and Figure 4.17).

Table 4.4.3.1 Patients who experienced common adverse events in the 6 weeks studies

Dyskinesia				
Study	**Number of patients who experienced AE / Number of patients who received tolcapone (200 mg)**	**Number of patients who experienced AE / Number of patients who received placebo**	**RR (95% CI)**	**M-H Weight**
Adler et al. (1998)	49 / 74	14 / 72	3.41 (2.13, 5.67)	7.10
Kurth et al. (1997)	20 / 40	9 / 42	2.33 (1.25, 4.55)	4.39
Myllyla et al. (1997)	13 / 38	7 / 42	2.05 (4.58, 3.33)	3.33
Pooled estimate (Rothma-Boice)			2.78 (1.95, 3.97)	
Chi-square for pooled relative risk			32.09 (df = 1) P < 0.0001	
Q "non-combinability" for relative risk			1.46 (df = 2) P = 0.4831	
Pooled estimate (DerSimonian-Laird)			2.76 (1.93, 3.94)	
DerSimonian-Laird Chi-square			31.29 (df = 1) P < 0.0001	
Dizziness				
Adler et al. (1998)	4 / 74	6 / 72	0.67 (0.22, 2.02)	3.29
Kurth et al. (1997)	3 / 40	0 / 42	7.26 (0.72, 77.65)	0.24
Myllyla et al. (1997)	0 / 38	0 / 42	N/A	0.24
Pooled estimate (Rothma-Boice)			1.13 (0.44, 2.92)	
Chi-square for pooled relative risk			0.07 (df = 1) P = 0.798	
Q "non-combinability" for relative risk			2.33 (df = 2) P = 0.3112	
Pooled estimate (DerSimonian-Laird)			1.09 (0.29, 4.06)	
DerSimonian-Laird Chi-square			0.016 (df = 1) P = 0.8994	

RR: Rate Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach uses DerSimonian and Laird method

Table 4.4.3.1 Patients who experienced common adverse events in the 6 weeks studies (cont.)

Nausea				
Study	**Number of patients who experienced AE / Number of patients who received tolcapone (200 mg)**	**Number of patients who experienced AE / Number of patients who received placebo**	**RR (95% CI)**	**M-H Weight**
Adler et al. (1998)	21 / 74	8 / 72	2.55 (1.25, 5.36)	4.05
Kurth et al. (1997)	10 / 40	5 / 42	2.1 (0.83, 5.49)	2.44
Myllyla et al. (1997)	10 / 38	1 / 42	11.05 (1.97, 65.58)	0.48
Pooled estimate (Rothma-Boice)			2.97 (1.70, 5.21)	
Chi-square for pooled relative risk			14.47 (df = 1) P = 0.0001	
Q "non-combinability" for relative risk			2.28 (df = 2) P = 0.3193	
Pooled estimate (DerSimonian-Laird)			2.74 (1.45, 5.16)	
DerSimonian-Laird Chi-square			9.73 (df = 1) P = 0.0018	
Vomiting				
Adler et al. (1998)	5 / 74	0 / 72	10.7 (1.08, 109.43)	0.25
Kurth et al. (1997)	0 / 40	0 / 42	N/A	0.25
Myllyla et al. (1997)	3 / 38	0 / 42	7.73 (0.76, 81.64)	0.24
Pooled estimate (Rothma-Boice)			6.49 (1.17, 35.92)	
Chi-square for pooled relative risk			4.59 (df = 1) P = 0.0321	
Q "non-combinability" for relative risk			0.97 (df = 2) P = 0.6154	
Pooled estimate (DerSimonian-Laird)			5.70 (0.93, 35.06)	
DerSimonian-Laird Chi-square			3.53 (df = 1) P = 0.0604	

RR: Rate Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach uses DerSimonian and Laird method

Table 4.4.3.1 Patients who experienced common adverse events in the 6 weeks studies (cont.)

Urine discolouration				
Study	**Number of patients who experienced AE / Number of patients who received tolcapone (200 mg)**	**Number of patients who experienced AE / Number of patients who received placebo**	**RR (95% CI)**	**M-H Weight**
Adler et al. (1998)	8 / 74	1 / 72	5.51 (1.20, 26.09)	0.76
Kurth et al. (1997)	9 / 40	0 / 42	19.94 (2.14, 196.96)	0.24
Myllyla et al. (1997)	0 / 38	0 / 42	N/A	0.24
Pooled estimate (Rothma-Boice)			7.47 (2.04, 27.40)	
Chi-square for pooled relative risk			9.21 (df = 1) P = 0.0024	
Q "non-combinability" for relative risk			1.52 (df = 2) P = 0.4684	
Pooled estimate (DerSimonian-Laird)			6.13 (1.56, 24.01)	
DerSimonian-Laird Chi-square			6.77 (df = 1) P = 0.093	

RR: Rate Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach uses DerSimonian and Laird method

Table 4.4.3.2 Patients who experienced common adverse events in the 12 weeks studies

Dyskinesia				
Study	**Number of patients who experienced AEs / Number of patients who received tolcapone (200 mg)**	**Number of patients who experienced AEs / Number of patients who received placebo**	**RR (95% CI)**	**M-H Weight**
Baas et al. (1997)	31 / 59	12 / 58	2.54 (1.48, 4.49)	6.05
Rajput et al. (1997)	43 / 67	12/ 66	3.53 (2.12, 6.14)	6.04
Pooled estimate (Rothma-Boice)			3.03 (2.06, 4.47)	
Chi-square for pooled relative risk			31.37 (df = 1) P < 0.0001	
Q "non-combinability" for relative risk			0.69 (df = 1) P = 0.4067	
Pooled estimate (DerSimonian-Laird)			3.01 (2.04, 4.44)	
DerSimonian-Laird Chi-square			30.78 (df = 1) P < 0.0001	
Sleep disorder				
Baas et al. (1997)	12 / 59	10 / 58	1.18 (0.56, 2.49)	5.04
Rajput et al. (1997)	19 / 67	15 / 66	1.25 (0.70, 2.24)	7.56
Pooled estimate (Rothma-Boice)			1.22 (0.77, 1.94)	
Chi-square for pooled relative risk			0.71 (df = 1) P = 0.3994	
Q "non-combinability" for relative risk			0.01 (df = 1) P = 0.9084	
Pooled estimate (DerSimonian-Laird)			1.22 (0.77, 1.94)	
DerSimonian-Laird Chi-square			0.72 (df = 1) P = 0.3965	

RR: Rate Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach uses DerSimonian and Laird method

Table 4.4.3.2 Patients who experienced common adverse events in the 12 weeks studies (cont.)

Nausea				
Study	**Number of patients who experienced AE / Number of patients who received tolcapone (200 mg)**	**Number of patients who experienced AE / Number of patients who received placebo**	**RR (95% CI)**	**M-H Weight**
Baas et al. (1997)	17 / 59	8 / 58	2.09 (1.01, 4.44)	4.03
Rajput et al. (1997)	24 / 67	16/ 66	1.48 (0.87, 2.53)	8.06
Pooled estimate (Rothma-Boice)			1.68 (1.09, 2.60)	
Chi-square for pooled relative risk			5.45 (df = 1) P = 0.0196	
Q "non-combinability" for relative risk			0.54 (df = 1) P = 0.4624	
Pooled estimate (DerSimonian-Laird)			1.66 (1.07, 2.56)	
DerSimonian-Laird Chi-square			5.15 (df = 1) P = 0.0233	
Vomiting				
Baas et al. (1997)	5 / 59	2 / 58	2.46 (0.57, 10.71)	1.01
Rajput et al. (1997)	0 / 67	0/ 66	N/A	0.26
Pooled estimate (Rothma-Boice)			2.16 (0.50, 9.32)	
Chi-square for pooled relative risk			1.07 (df = 1) P = 0.3018	
Q "non-combinability" for relative risk			0.18 (df = 1) P = 0.6712	
Pooled estimate (DerSimonian-Laird)			2.16 (0.49, 9.47)	
DerSimonian-Laird Chi-square			1.03 (df = 1) P = 0.3092	

RR: Rate Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haenszel method
Random effect approach uses DerSimonian and Laird method

Table 4.4.3.1 Patients who experienced common adverse events in the 12 weeks studies (cont.)

Urine discolouration				
Study	**Number of patients who experienced AE / Number of patients who received tolcapone (200 mg)**	**Number of patients who experienced AE / Number of patients who received placebo**	**RR (95% CI)**	**M-H Weight**
Baas et al. (1997)	0 / 59	0 / 58	N/A	0.26
Rajput et al. (1997)	8 / 67	0 / 66	16.75 (1.74, 166.96)	0.25
Pooled estimate (Rothma-Boice)			8.80 (1.14, 68.02)	
Chi-square for pooled relative risk			4.34 (df = 1) P = 0.0372	
Q "non-combinability" for relative risk			1.41 (df = 1) P = 0.2353	
Pooled estimate (DerSimonian-Laird)			5.55 (0.34, 90.45)	
DerSimonian-Laird Chi-square			1.45 (df = 1) P = 0.2291	

RR: Rate Ratio
M-H weight: Mantel-Haenszel
Fixed effect approach uses Mantel-Haensel method
Random effect approach uses DerSimonian and Laird method

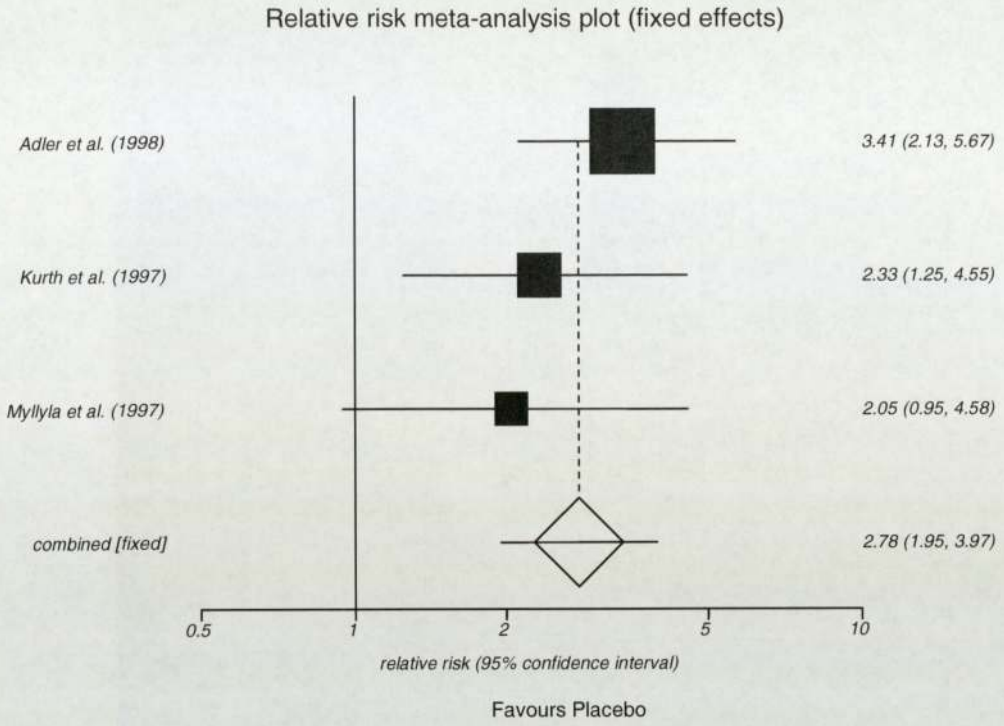


Figure 4.8 Rate ratio of dyskinesia in the 6 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see the legends under Figure 4.3, page 91.)

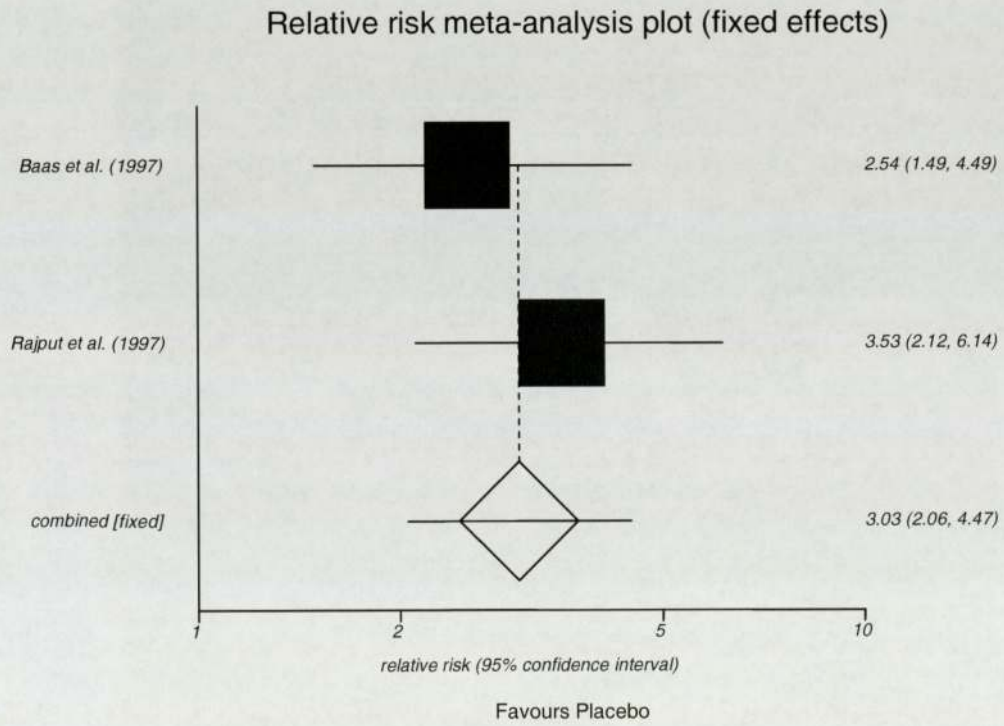


Figure 4.9 Rate ratio of dyskinesia in the 12 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see the legends under Figure 4.4, page 92.)

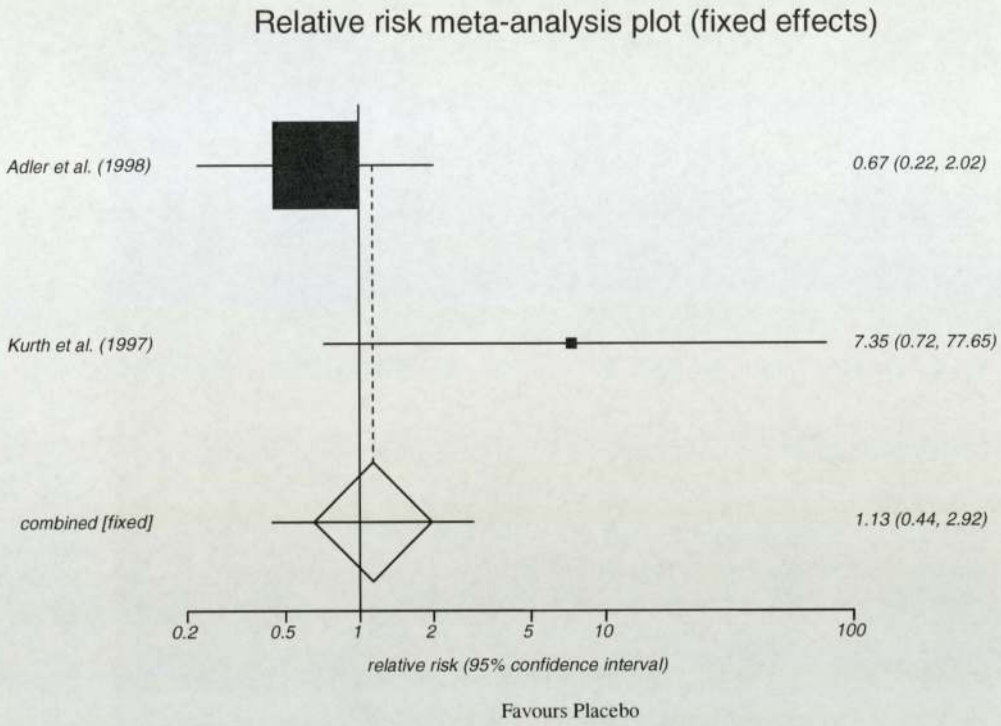


Figure 4.10 Rate ratio of dizziness in the 6 weeks trial comparing tolcapone and placebo. (For explanations of the symbols see the legends under Figure 4.3, page 91.)

The pooled relative risk for this analysis was very close to the line of no effect when the 200 mg tolcapone group and the placebo group were compared. This is because the number of patients who experienced dizziness in the placebo group was slightly more than in the 200 mg tolcapone group, although the total number of patients who experienced dizziness was more in the tolcapone group than in the placebo group.

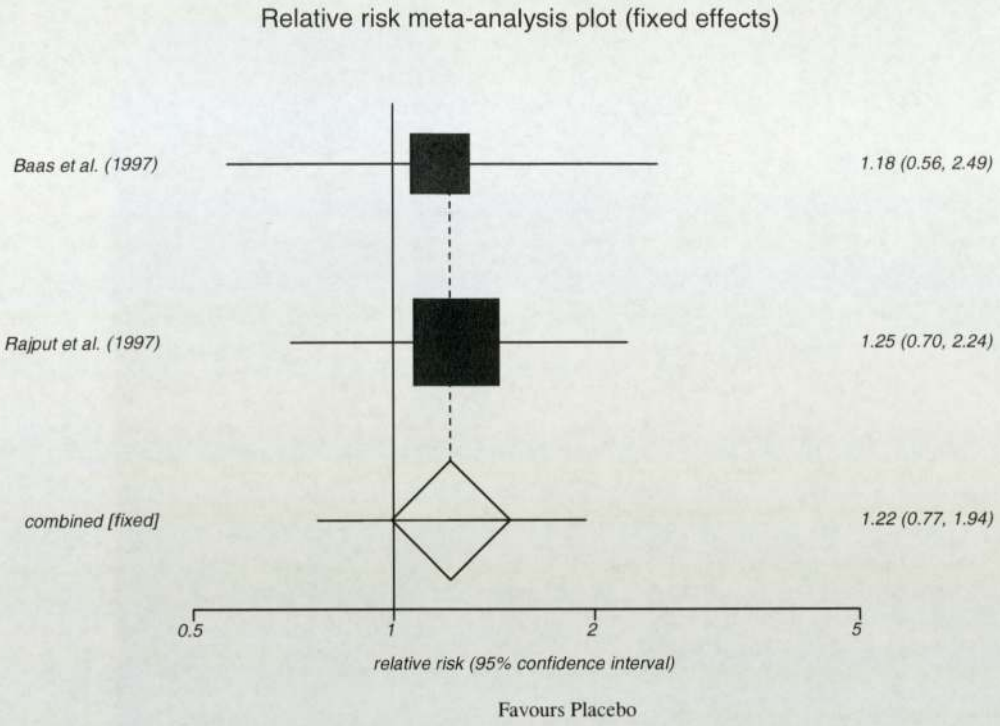


Figure 4.11 Rate ratio of sleep disorder in the 12 weeks trial comparing tolcapone and placebo. This figure shows a non-significant result in favour of placebo. (For explanations of the symbols see the legends under Figure 4.4, page 92.)

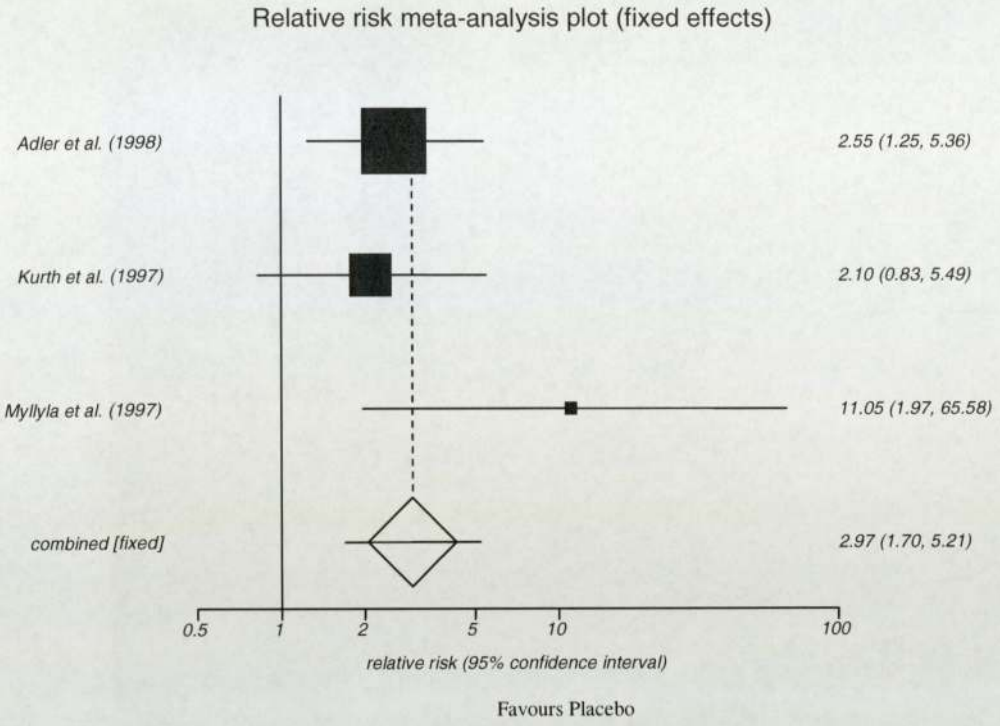


Figure 4.12 Rate ratio of nausea in the 6 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see legends under Figure 4.3, page 91.)

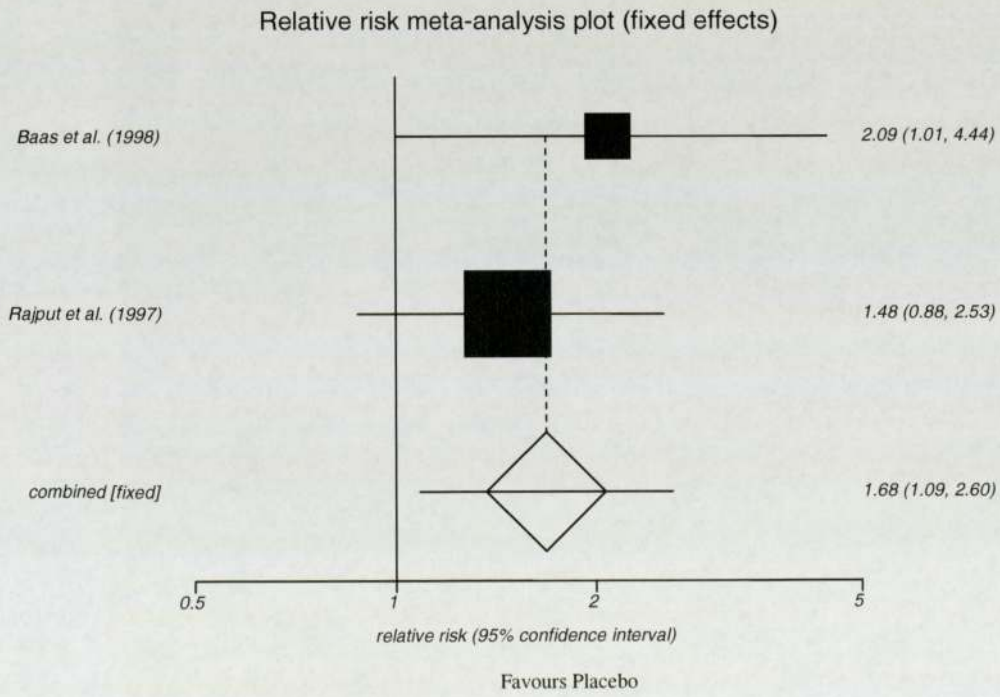


Figure 4.13 Rate ratio of nausea in the 12 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see the legends under Figure 4.4,page 92.)

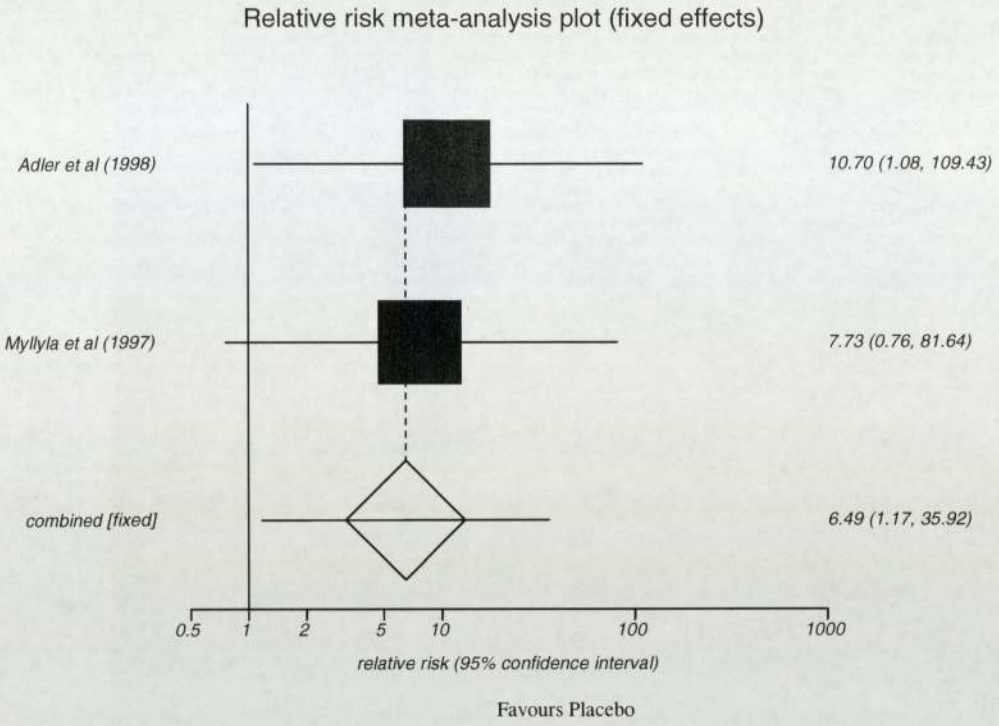


Figure 4.14 Rate ratio of vomiting in the 6 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see the legends under Figure 4.3, page 91.)

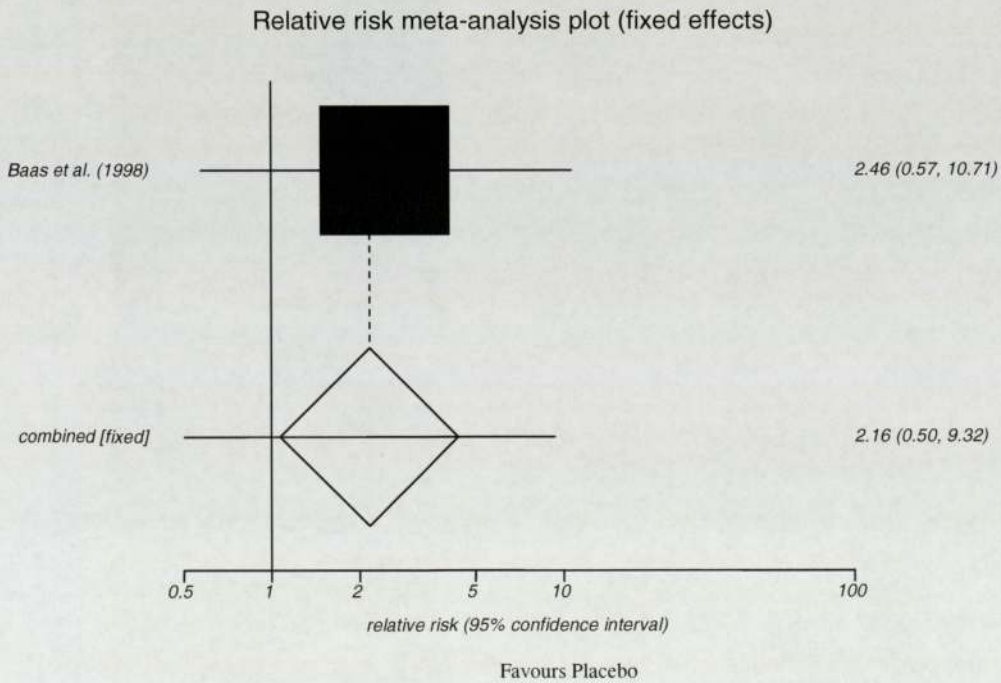


Figure 4.15 Rate ratio of vomiting in the 12 weeks trial comparing tolcapone and placebo. This figure shows a non-significant result in favour of placebo. (For explanations of the symbols see the legends under Figure 4.4, page 92.)
No vomiting reported in Rajput et al. (1997)

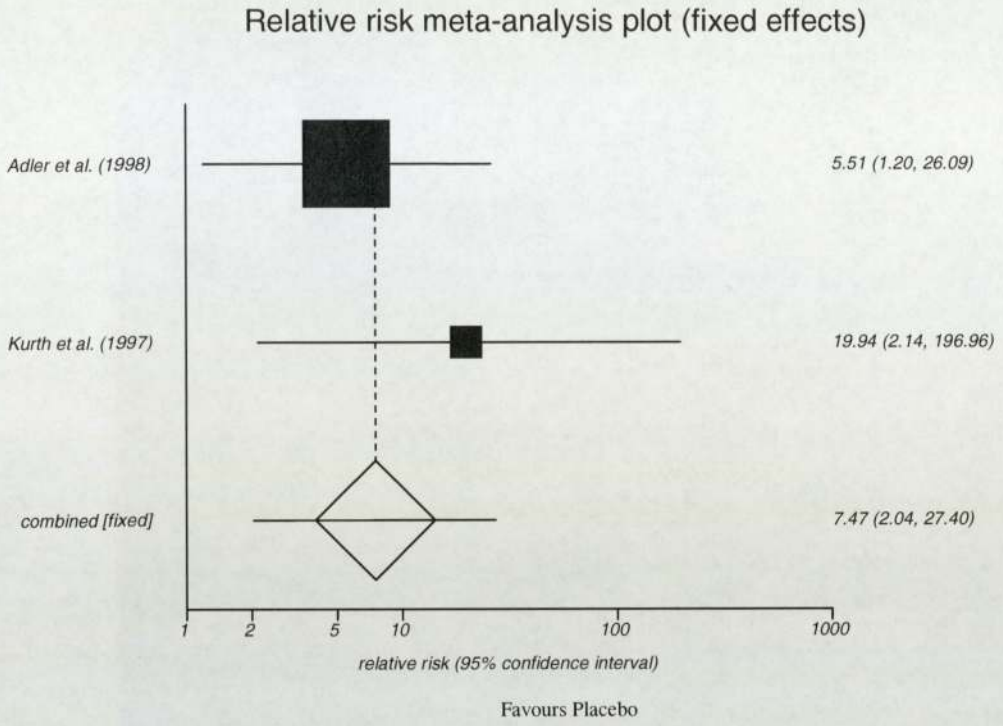


Figure 4.16 Rate ratio of urine discolouration in the 6 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see legends under Figure 4.3, page 91.)

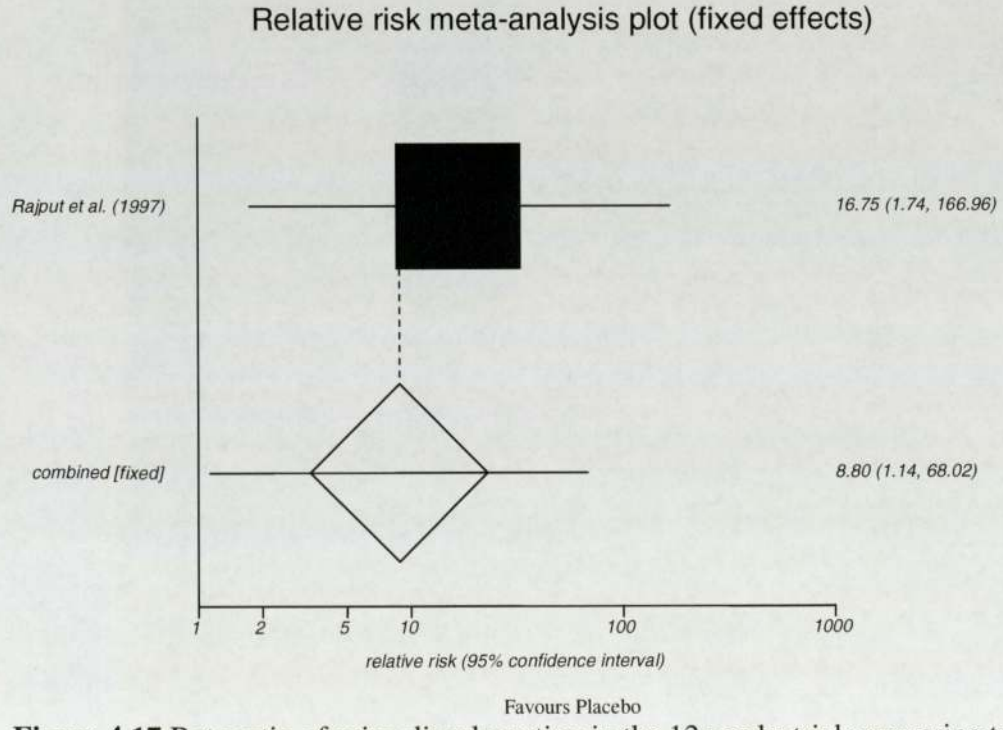


Figure 4.17 Rate ratio of urine discolouration in the 12 weeks trial comparing tolcapone and placebo. This figure shows results in favour of placebo. (For explanations of the symbols see legends under Figure 4.4, page 92.)
No urine discolouration reported in Baas et al. (1997)

4.4.4 Discussion and Conclusion

In terms of changes in daily L-dopa dose, the results are consistent across the studies investigated. The daily L-dopa dose reduction for tolcapone showed significant heterogeneity (P = 0.0001). The "on" time increase was available in all 3 studies (Adler et al., 1998, Kurth et al., 1997, Myllyla et al., 1997) at the 6 week assessment and 1 study (Baas et al., 1997) at the 12 week assessment. The analysis of the 6 week assessment showed no significant heterogeneity between the studies. As the "on" time result was available only in the study of Baas et al. (1997), the analysis for the 12 week assessment could not be performed. The "off" time reduction was available for all 5 studies. Both the 6 week and 12 week assessment showed " off" time "not significant" for the 2 groups (P = 0.5239, P = 0.1894, respectively).

The opposite withdrawal results are seen in the 6 week and 12 week assessment studies. This suggests that 6 weeks is too short a time to evaluate the studies.

As far as adverse events are concerned, the patients who received tolcapone experienced dopaminergic events more often than those who received placebo.

CHAPTER 5

DISCUSSION

5.1 General

Catechol-O-methyltransferase (COMT) is one of the main enzymes metabolizing L-dopa, dopamine, other catecholamines (adrenaline and noradrenaline), and their metabolites. L-dopa is metabolized by several different enzymes, with dopa decarboxylase also playing a large part. When L-dopa is administered with a peripheral dopa decarboxylase inhibitor such as carbidopa or benserazide, COMT predominates in L-dopa metabolism leading to 3-O-methyldopa (3-OMD), a compound, which may decrease L-dopa absorption and efficacy. All of the published pharmacokinetic studies show that tolcapone (Tasmar®) does not change Cmax but increases L-dopa half life and the area under the curve (AUC) (Jorga et al., 1998).

Tolcapone and entacapone, are both catechol-o-methyl-transferase (COMT) inhibitors. Tolcapone was approved in 1998 and entacapone in 1999, for the treatment of fluctuating Parkinson's disease (Factor et al., 2001). Although these drugs are in the same class, they have some pharmacological differences. For instance, tolcapone has a greater bioavailability and AUC and leads to longer COMT inhibition. There have been no direct studies comparing tolcapone and entacapone clinically. However, many similar clinical studies have been performed for the two drugs with similar outcomes.

The results of the studies in the present study show that the addition of tolcapone to L-dopa / carbidopa or benserazide, increased "on" time and decreased "off" time, and decreased the L-dopa daily dose significantly compared with the placebo. In the studies, in the tolcapone groups the "on" time increased from the baseline by 2 hours per day on average, and the "off" time also decreased by 2 hours on average. This means that motor fluctuation improved when tolcapone was added to L-dopa / carbidopa or benserazide in patients with fluctuating Parkinson's disease. The use of tolcapone is therefore worth considering as an important therapy option.

Shan et al. (2001) was excluded for meta-analysis in the present study as the tolcapone group results were not reported for 100 mg and 200 mg separately. In the study of Shan et al. (2001) the patients received either placebo or 100 mg tolcapone in the first instance. The tolcapone dose was increased to 200 mg 3 weeks after the start of the trial if further improvement was expected. Five patients remained on 100 mg tolcapone as they gained a marked improvement on this dose. For "off" time, Shan et al. (2001) reported a significant difference between the tolcapone and the placebo groups.

Shan et al. (2001) stated that although the UPDRS III score improved significantly during "off" time, there was no additional benefit during "on" time while only Baas et al. (1997) stated that there was a significant difference ($P < 0.01$). However, the UPDRS III score decreased more in the tolcapone group in all of the studies. As no studies stated when the UPDRS III score was measured, it is assumed that it was measured during "on" time. This score was assessed by interview, and it may have been very difficult to see a significant change in the patient's movement before and after tolcapone was administered within the limited study period. However, Parkinson's disease is a progressive disease. Tolcapone does not appear to be able to halt its progression and it seems that it cannot cure it.

5.2 Hepatotoxicity

Hepatotoxicity is one of the most important adverse events pharmaceutical companies have to be aware of and concerned about. Many newly discovered drugs have been withdrawn or new approval denied because of hepatotoxicity. Table 5.2.1 below shows a few well-known examples.

Table 5.2.1 Hepatotoxicity through the years (adapted from : Robert J Temple. Impact on the FDA; http://www.fda.gov/cder/livertox/presentations/im1389/sld001.htm.)

Withdrawal	Non-Approval
Marsilid (1956)	Ibufenac (1920)
Ticiynafen (1979)	Perhexiline (1980)
Benoxaprofen (1982)	Dilevalol (1990)
Bromfenac (1998)	Tososortan (1998)
Troglitizone (2000)	

Apart from non-approved and withdrawn drugs, many agents are explicitly second-line or bear serious warnings because of liver toxicity. In the U.S.A, tolcapone is classed as a second-line drug. A second-line drug is an agent which is still marketed but severely restricted in its applications.

While a relationship with a pre-existing liver disease is often suspected, direct evidence is often lacking. Hepatotoxicity is often an individual idiosyncratic reaction. It is very important to be aware of the risk of hepatotoxicity to prevent a drug-induced tragedy.

The liver is very easily damaged by drugs because of its unique role in removing toxic substances from the blood. The best evidence of a hepatotoxic problem is an increased level of transaminase to more than three times the upper limit of the normal range. Some patients showed liver damage through elevation of bilirubin without evidence of

obstruction and elevated alkaline phosphatase. The reason why transaminase and bilirubin are good markers is that hepatocellular damage is highly likely to impair bilirubin excretion. Also about 10 % of patients with elevated transaminase and jaundice will have serious and eventually fatal hepatic complications (www.fda.gov). The signs of liver damage are abnormally yellow skin and eyes as a result of impaired bilirubin excretion, dark urine, light-coloured stools, nausea, vomiting and loss of appetite. The question is then how rare or mild the hepatotoxicity is and how great the benefits of the drug are to patients. These first two considerations are essential. It is then also important to consider how frequently hepatotoxicity occurs, how preventable or manageable it is and if there are any other treatments available for the disease. It is all a question of balancing risk and benefit.

Strangely, in most cases, the potential danger to the liver was not well recognised in the course of most pre-marketing clinical trials. Although four patients with Parkinson's disease developed severe hepatic dysfunction which was ascribed to tolcapone, only three pre-marketing studies (Baas et al., 1997, Rajput et al., 1997, Waters et al., 1998) mentioned liver enzyme elevation. Table 5.2.2 shows how liver abnormality was reported in the studies included in the present study.

Table 5.2.2 Reported liver abnormality in this research

Adler et al. (1998)	No consistent changes in laboratory test results.
Baas et al. (1997)	Tolcapone group: mean concentrations of AST and ALT were higher at week 6 than with placebo. These were considered by the investigators to be probably related to tolcapone treatment.
Kurth et al. (1997)	No change in liver function.
Myllyla et al. (1997)	No laboratory abnormalities were found that could be related to tolcapone.
Rajput et al. (1997)	Tolcapone treatment was associated with raised aspartate alanine aminotransferase concentrations in 3 patients in the 100 mg tolcapone group and 2 in the 200 mg tolcapone group. One of the latter withdrew from the study as a result.

Two studies which were identified during electronic search also reported that the results of the liver function test were not significant. Waters et al. (1998) reported that raised liver enzyme levels were the only laboratory abnormalities seen. Alanine aminotransferase was raised in 3 patients (3%) in the 100 mg tolcapone group and 5 patients (5%) in the 200 mg tolcapone group. Four of the affected patients (3 in the 200 mg tolcapone group) were withdrawn due to the raised liver enzyme concentrations. The remaining 4 patients returned to normal levels while on treatment. All cases developed within 6 months of starting treatment. Dupont et al. (1997) stated that no differences were seen between tolcapone and placebo in the results of the laboratory assessments. Just a few months before tolcapone was approved, Jorga et al. (1998) reported on its safety and tolerability in patients with moderate liver disease. The report stated that there had been no withdrawal from the study, and tolcapone had been well tolerated. Most adverse events had been considered to be mild and had occurred in all groups at a similarly low level. All events had resolved without sequelae and no serious events had

been reported in the study and it was concluded that the drug was safe for patients with moderate liver disease (Jorga et al., 1998). However, it appeared that tolcapone had been almost completely metabolised to the glucuronide metabolite. Because tolcapone binds strongly to plasma albumin, it is not easy to assess how much a pre-exisisting liver disease may effect the hepatic elimination of the drug (Jorga et al., 1998).

Following the FDA warning and withdrawal from EU countries, the use of tolcapone decreased dramatically (Figure 1.5). The manufacturing company did a safety surveillance program from 1998 to 2000 (Roche, 2000). Four hundred and seventy patients were enrolled in the study. The duration of the study was over a period of 18 months. The demographics and history of Parkinson's disease are shown in Table 5.2.3.

Table 5.2.3 Demographics and history of PD from the safety surveillance done by the manufacturing company (Adapted from Roche, Tasmar safety surveillance program, Final report, 2000)

Ratio of men to women: 2 : 1.
Median age (range): 70 years (33 – 94).
Mean age at onset of Parkinson's disease: 59 years (S.D. 10.7)
Mean duration of disease: 10 years (S.D. 5.9).

However, about one third of the patients left the study, and the most prominent reason for this was the decision of the physician. Also a new COMT inhibitor, entacapone, a new drug dopamine agonist (DA), non-ergoline derivative, pramipexole, and a new drug, dopamine agonist, ergot derivative, cabergoline, were introduced at this time. The company's report suggested that this was the most likely reason for the withdrawal of the patients from the study. Elevation of transaminase activities (ALT and / or AST > 100% upper normal limit (UNL) occurred in 76 patients (16.2 %). However, only 11 patients (2.3%)

showed an increase of more than 200 %. In the safety surveillance, transaminase activities were measured 4343 times. Approximately, 1 % of all the measurements of AST / ALT recorded elevations of transaminase activity over 150% of the UNL (Roche intranet).

As the PD patients were elderly, many of them had another risk factor, most commonly a disease, such as cancer. There are other possible causes including:

- Transaminase elevation (AST and / or ALT) associated with diseases or a concomitantly used drug
- If the outcome was death, this is a common event in this elderly age group.
- Other adverse events associated with the management of PD, and the progressive course of PD.

The safety surveillance shows that with appropriate precautions and relevant guidelines physicians are able to treat their patients with tolcapone with an acceptable benefit / risk ratio. Patients need to be observed and frequent checks of their transaminases are necessary. They need to report any changes in medications and to notify their physicians of any symptoms that may be an early indication of liver damage. Treating physicians need to be aware of the risks of liver damage. The present systematic review suggests that despite the adverse effects of tolcapone the drug has an acceptable risk-benefit profile in the treatment of fluctuating PD provided treatment guidelines suggested by the manufacturers are followed.

Factors to be considered:

Standard dose:

The recommended dose of tolcapone is 100 mg three times daily, always as an adjunct to

L-dopa/beserazide or L-dopa/carbidopa therapy. Only if clinical benefits outweigh the risk of hepatotoxicity should tolcapone be increased to 200 mg three times daily. The maximum therapeutic dose of 200 mg three times daily should not be exceeded, as there is no evidence of additional efficacy at higher doses.

Regimen:

Oral administration. The first dose of the day of tolcapone should be taken together with the first dose of the day of a L-dopa preparation, and the subsequent doses of tolcapone should be given approximately 6 and 12 hours later.

Liver function tests:

ALT and AST should be monitored before starting treatment with tolcapone and then every 2 weeks for the first year of the therapy, every 4 weeks for the next 6 months, and then every 8 weeks thereafter. If the liver enzyme values exceed the upper normal limit, tolcapone should be discontinued.

Other considerations:

When tolcapone therapy is started a reduction in the daily L-dopa dose should be considered to avoid increased dopaminegic reaction.

5.3 Limitation of the present study

A major limitation of this present study is that only a small number of studies were identified and included in the review. If individual patients' data was available, it would be possible to pool more data.

5.4 Future and further studies

An updated systematic review should be performed, as tolcapone has come back onto the European market, although with restrictions. In addition, meta-analysis of individual patient's laboratory data for liver function may be helpful for the reassessment of the hepatotoxicity related to tolcapone.

Appendix 1

Appendis 1-1: 182 relevant articles were identified and screened for retrieval

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Appendix 1-2: Identification by key words of "tolcapone and benserazide"

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Appendix 1-3: Identifications by key words of "tolcapone and carbidopa"

Reference List

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Appendix 1-4: Identification by key words of "tolcapone and randomised controlled trials"

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Appendix 2

Characteristics of included studies

Study Adler et al. (1998)

Methods	Randomised. Double blind Placebo controlled Parallel study Duration : 6 weeks Study assessments: at the end of week 6
Participants	country: U.S.A. and Canada Centre: 15 Inclusion criteria: had at least 2 of the cardinal signs of idiopathic Parkinson disease (rigidity, resting tremor, or bradykenesia), and had been treated with L-dopa for at least 1 year with clear clinical improvement Exclusion criteria: non-idiopathic Parkinson's disease or parkinsonian variants, sudden or unpredictable "on / off" fluctuations or dyphasic pattern of diskinesias. Treatment with centrally acting dopamine antagonists or monoamine oxidase inhibitors (other than selegiline) within the previous 2 months, drug or alcohol abuse within the previous 2 years, psychotic illness or major depression within the previous 6 months, and any other clinically significant medical or neurological abnormality. Number of patient: 215 Withdrawn: 12; 6 from placebo, 2 from 100 mg, 4 from 200 mg. Mean age: 62 Male : Female: 149 : 66 Mean disease duration: 10 years
Interventions	In addition to their usual L-dopa / carbidopa regimen, patients received placebo or tolcapone 100 or 200 mg TID PO
Outcomes	Efficacy and safety of the study drug were assessed between baseline (the day before study medication was first administered) and week 2, 3, and 6 (+/- 3 days). Results at 6 weeks were given. • Tolcapone 100, 200 mg TID reduced "off" time by 2.0 and 2.5 mg per day, respectively • Increased "on" time by 2.1 and 2.3 hours per day, respectively. • Investigators' global measures of disease severity indicated that significantly more of the tolcapone treated group had reduced wearing-off and severity.

- No significant change in quality of life measures (UPDRS II) occurred.
- Clinical improvements occurred despite a reduction in total daily L-dopa dose of 185.5 mg (23 %) in the tolcapone 100 mg group and 251.5 mg (29%) in the 200 mg group.
- Worsening of dyskinesia, as with most dopaminergic symptoms, occurred most often at the start of treatment.
- The frequency of withdrawals because of adverse events was similar in all groups (3 % - 7%).

Conclusions — Tolcapone was well tolerated and substantially increased "on" time and reduced "off" time in patients with fluctuating Parkinson's disease. Additionally, L-dopa requirements were significantly decreased.

Study Baas et al. (1997)

Methods

Randomised.
Double blind
Placebo controlled
Parallel study
Duration : 12 months
Study assessments: the primary end point was 12 weeks.

Participants

Country: Europe
Centre: 24
Inclusion criteria: patients with at least two of the three cardinal features of Parkinson's disease (bradykinesia, resting tremor and rigidity) and who exhibited predictable end of dose motor fluctuations in response to L-dopa therapy.
Exclusion criteria: patients with non-idiopathic parkinsonism, patients who had undergone neurological surgery during the previous year, treatment with any of following medications: a centrally acting dopamine antagonist during the preceding six months, monoamine oxidase inhibitor (except selegiline) in the preceding two months, apomorphine in the preceding seven days, or any investigational agents within the preceding four weeks.
Number of patients: 177
Withdrawn: 27 : 4 from placebo, 14 from 100 mg, 9 from 200 mg.
Mean age: 63
Male: Female: 99 : 78
Mean disease duration: 9.8 years

Interventions

Patients were randomised to receive either placebo or 100 or 200 mg tolcapone three times daily.
LD: L-dopa / benserazide

Outcomes

After 3 months with tolcapone 200 mg tid.

- " off" time increased by 20.6 % from the baseline value.
- "on" time increased by 20.5 % from the baseline value.
- mean total daily L-dopa dose decreased by 122 mg from baseline dose of 676 mg.
- UPDRS motor and total scores were significantly reduced
- quality of life (sickness impact profile) scores were significantly improved.

These responses were maintained up to nine months.

After 3 months with 100 mg tolcapone TID

- "off-time" decreased by 31.5 %
- "on-time" increased by 21.3%
- mean total daily L-dopa dose decreased by 109 mg from the base line dose of 668 mg.

Adverse event:

- Both 100, 200 mg were well tolerated.
- Dyskinesia was the most often reported L-dopa induced adverse event.
- Diarrhoea was the most often reported non-dopaminegic adverse event and the most frequent reason for withdrawal from the study.
- Tolcapone group, mean concentration of AST and ALT were higher at week 6 than with placebo. These considered by investigator to be probably related to tolcapone treatment.

Conclusion: Tolcapone prolongs "on-time" in fluctuating parkinsonian patients while allowing a reduction in daily L-dopa dosage, thereby improving the efficacy of long term L-dopa therapy.

Study Kurth et al. (1997)

Methods

Randomised
Double blind
Placebo controlled
Parallel study
Duration: 6weeks

Participants

Country: U.S.A.
Centre: 12
Inclusion criteria: Only patients with idiopathic PD occurring after age 30, experiencing a predictable "on" response to the first morning dose of L-dopa / carbidopa, with at least two episodes of predictable end of dose "off" periods were eligible. The total "off" time while awake had to

exceed 2 hours per day. Patients were on a stable regimen of at least three doses per day of standard Sinemet 25-100 tablets.
Exclusion criteria: All those not described above. Patients were excluded if they experienced unpredictable motor fluctuations. Treatment with dopamine agonists, amantadine, anticholinergics, selegiline, carbidopa or L-dopa alone, Sinemet alone, Sinemet CR, Sinemet 1:10 ratio, and agents used to treat tremor (primidone, beta-blockers) was not allowed.
Number of patients: 161
Withdrawn: 10 (5 due to adverse events)
Mean age: 64.5
Male: Female: 105 : 56
Mean disease duration: 9.23 years

Interventions

During the single-blind, baseline period:
patients took placebo tablets tid; patients underwent a 10-hour (8 am – 6 pm) assessment; the investigator examined each patient using the UPDRS motor scale, the "on/off" rating scale, and the diskinesia rating scale, and then administered the first dose of sinemet and the single-blinded test medication (placebo).
During the double-blind treatment period:
patients who entered the treatment period were randomised to either placebo or one of three tolcapone doses (50 mg, 200 mg, or 400 mg tid) and instructed to take the test medication at 6-hour intervals while awake. The first dose was taken with sinemet. Once patients started the treatment period, the sinemet dose could be adjusted, but could not exceed the baseline intake. No changes or adjustments in sinemet were permitted after day 28. Patients returned to the clinic on day 7, 14, 28 and 42.

Outcomes

Primary measures: (investigator's 10-hour evaluation of "off-time".

- Mean "off-time" during the investigator assessed 10 hour evaluation showed a significant decline at all doses of tolcapone compared to the placebo between the baseline and week 6. Changes in "off-time" as a percentage of the 10 hour day were decreased by approximately 1.5 hours, or 40 % of baseline "off-time" in all tolcapone groups.
- Mean UPDRS motor score:
  No significant differences between the placebo group and any dose group of tolcapone were observed in patients examined using the UPDRS subscales I, II, or III when "on-time" was at the baseline and at week 6. However, figures which show the mean UPDRS motor score (y-axis) for each time plotted against the time of the day (x-axis) show that the group of patients who took a higher tolcapone dose 400 mg had a marked lower UPDRS motor score.

Secondary measures : (investigator's 10-hour evaluation of "on-time" and "on-time" with dyskinesia.

- The tolcapone treatment group showed a significant increase while no change occurred in the placebo group.

L-dopa dosages:

- A significant reduction of the daily L-dopa dose was noted for every dose group with tolcapone compared to the placebo group.

Adverse event:

- Treatment was well tolerated.
- Adverse events were typically dopaminergic and could be minimized or eliminated by reduction of L-dopa / carbidopa.
- No differences in efficacy were noted in patients who experienced adverse events at higher frequencies with tolcapone compared to the placebo as compared to those without adverse events.

Conclusion:

- The investigator's evaluation at week 6 of overall efficacy, wearing-off, and severity of PD showed that all doses of tolcapone improved the condition of PD patients.
- Only with the highest dose of tolcapone did a significant increase in dyskinesia become noted on that portion of the investigator's global assessment of change.
- There was a significant reduction in the UPDRS motor AUC with all three doses of tolcapone. The dose of tolcapone 200 mg tid offered the largest reduction in the motor UPDRS AUC.
- Other outcome measures, including patients' diaries, further support the efficacy of tolcapone in decreasing motor fluctuations in patients with PD treated with sinemet (100/25 mg).

Study Myllyla et al. (1997)

Methods

Randomised.
Double blind.
Placebo controlled.
Parallel study.
Duration: 6 weeks.

Participants

Country: Europe and Australia
Centre: 22 centres
Inclusion criteria: aged 40 years or more, had clinically idiopathic Parkinson's disease, and presented with the "wearing-off" phenomenon despite "optimal" antiparkinsonian therapy, with "off-time" comprising more than 25 % of the waking day, despite at least five daily doses of L-dopa. Patients were required to have received therapy with L-dopa/

decarboxylase inhibitor for at least 2 years and to have reached or almost reached the threshold of tolerability of L-dopa, shown by mild-to moderate dyskinesia or newly occurring dyskinesia after a slight increase in L-dopa dosage. Patients had to have been receiving a stable dosage of a standard L-dopa/decarboxylase inhibitor formulation, in a 4:1 ratio, for at least 2 months before enrolment, although a bedtime dose of a slow-release formulation was permitted. Disease severity during "on-time" of no more than 3 on the Hoehn and Yahr scale was admissible. Patients were required to be able to keep reliable "on/off" charts, alone or with family assistance, and were required to be motivated and reliable in this respect.

Exclusion criteria: Female patients who had not been amenorrhoeic for at least 1 year or surgically sterile for at least 6 months because of the risk of pregnancy. Patients who presented with non-idiopathic parkinsonism, predominantly trembling symptomatology therapy, unpredictable motor fluctuations, or diphasic dyskinesia in response to L-dopa. Patients also excluded were: patients being treated with L-dopa alone, L-dopa/carbidopa in a 10:1 ratio, L-dopa in a controlled released form during the daytime, in a total daily dose of more than 1200 mg (the highest daily dose recommended in many European countries), fewer than five or more than eight daily intakes, receiving treatment with neuroleptics, antidepressants (except low-dose tricyclic antidepressants at bedtime), selegiline, or any investigational drug within the preceding 2 months, apomorphine in the preceeding week, antiemetics, high protein-binding drugs (> 90%), moderately high protein binding drugs with narrow therapeutic range, patients who presented with unstable medical problems, significant organic disease or related treatment, a history of alcoholism, drug abuse, evidence of previous myocardial infarction, arrhythmia, conductance defects on ECG (electrocardiography).

Number of patients: 154
Number withdrawn: 10
Mean age: 62.5
Male : Female: 95 : 59
Mean disease duration: N/A

Interventions

After the placebo run-in period, patients were randomised in double-blind manner to one of four groups, to receive the placebo or tolcapone 50, 200 or 400 mg tid orally for 6 weeks. The baseline was defined as the start of this study. The first dose of tolcapone or placebo of the day was taken with the first dose of L-dopa. The second and third dose of the study medication were taken at 6 hourly intervals thereafter Patients continued receive their usual regimen of L-dopa /decarboxylase inhibitor (unless L-dopa dosage adjustment was deemed necessary). L-dopa therapy could not be changed during the placebo run in period or the first day of double-blind treatment.

Outcomes

- Primary efficacy: Change in L-dopa dose from baseline to week 6. Great reduction in daily L-dopa intake occurred in the 200 mg tid tolcapone group.
  L-dopa dose was reduced in
  12 % in the placebo group
  32 % in the tolcapone 50 mg group
  34 % in the tolcapone 200 mg group
  14 % in the tolcapone 400 mg group
- Patients whose the dose was reduced experienced greater increases in "on-time" and decreases in "off-time" than patients with no dosage reduction.
- The greatest decrease in "off-time" was seen with tolcapone 200 mg tid.
- Secondary efficacy: "wearing-off"
  The number of patients who experienced improvement in "wearing – off" phenomena was greater in all the tolcapone treatment groups than the placebo group. The greatest improvement was seen with 200 mg tolcapone.
- None of the scores for UPDRS group scales I-III were statistically different from the placebo in tolcapone treated groups. However, the greatest improvement was seen in scores of II and III at doses of 200 and 400 mg tolcapone tid.
  UPDRS I:
  UPDRS II: activities of daily living
  UPDRS III: motor function
- Serious adverse events were unusual, occurring in 4 patients in the tolcapone 200 mg tid group and one each in the other groups. (hallucination and confusion occurred in 2 patients in the tolcapone 200 mg tid group, resulting in hospitalisation.)
- The rate of withdrawal was similar among the 4 groups. 10 patients withdrew from the study as a result of adverse events: 3 from the placebo group (rash; distonia; nausea), 2 from the tolcapone 50 mg tid group (panic reaction; aggressive reaction; aggravated parkinsonism), 1 from the tolcapone 200 mg tid group (enlarged prostate), and 3 from the 400 mg tid group (mealier; abdominal pain; nausea; vomiting; hallucination).
- Incidence of non-dopminergic adverse events was low. The most frequent adverse events were L-dopa-induced events.
  Dyskinesia worsened in 13 % of the placebo group, 20 % of the 50 mg tolcapone tid group, 19 % of the tolcapone 200 mg tid group, and 15 % of the 400 mg tolcapone tid group.
- Differences in incidence between the placebo and each tolcapone dosage group were too small for a relationship with tolcapone to be established.

Conclusion:

- Tolcapone 200 mg tid increased "on" time from 37.9% of the waking day to 50.8% ($p<0.01$) and reduced "off-time" from 26.7% of the waking day to 16.4% ($p<0.05$).
- Tolcapone treatment was generally well tolerated at all dosages.
- Initial exacerbation of adverse dopaminergic effects was controlled by L-dopa dosage adjustment; at week 6, the mean total daily L-dopa dosage had decreased by 80 mg, from 694 mg at the baseline, in the 200 mg tid group ($p<0.01$).
- The addition of tolcapone to L-dopa plus a decarboxylase inhibitor effectively and safely reduces the "wearing-off" phenomenon in parkinsonian patients.

Study Rajput et al. (1997)

Methods

Randomised.
Double blind.
Placebo controlled.
Parallel study.
Duration: 12 months.
Study assessment: the primary end point was 12 weeks.

Participants

Country: U.S.A. & Canada
Centre: 11
Inclusion criteria: Patients were at least 30 years of age, had 2 of 3 cardinal features of Parkinson's disease (rigidity, resting tremor, bradykinesia), and were clinically diagnosed as having idiopathic Parkinson's disease. Patients had to have been treated with L-dopa for at least 1 year and had to have shown clear improvement in parkinsonian symptoms with L-dopa. Patients had to be receiving at least four daily intakes of the standard L-dopa/carbidopa preparation or if controlled-release formulation was being used, at least 3 daily intakes. Patient had to have predictable motor fluctuations at the end of the dosing interval that could not be eliminated by adjusting the existing antiparkinsonian therapy.
Exclusion criteria: included nonidiopathic parkinsonism, sudden unpredictable "on-off" fluctuations or disabling diphasic dyskinesias, Mini-Mental State Examination score of 25 or less, and treatment with centrally acting dopamine antagonists during the previous 6 months or monoamine oxidase inhibitors (other than selegiline) during the previous 2 months.
Number of Patients: 202
Withdrawn: 37
Mean age: 64
Male : Female: 139 : 63
Mean disease duration: 10.87 years.

Intervention

After baseline assessment, patients (treated with stable dosages of L-dopa / carbidopa) were randomised to receive placebo or 100 mg or 200 mg tolcapone tid. During the first day of the study, the L-dopa dose could not be changed. After the first day, the dosage of L-dopa could be decreased as necessary if there was a L-dopa related adverse event. The L-dopa dose could not be increased to greater than the baseline dose during the first 3 months to allow for the efficacy of tolcapone. After month 3, the L-dopa dosage could be increased to exceed the baseline dose if necessary.

Outcomes

- The dosage of L-dopa was significantly reduced in patients receiving either dosage of tolcapone compared with those receiving the placebo ($p<0.01$).
- The number of daily doses was also significantly reduced ($p<0.01$).
- The duration of daily "off" time was reduced from the baseline in both doses of 100 mg and 200 mg tolcapone. However the change was significant only in the 200 mg tolcapone group ($p<0.01$) (3.25 hour reduction in daily "off-time" on average, according to the patients' daily diaries).
- The "wearing-off" phenomenon was reduced in 68 % of patients in the 100 mg tolcapone group and in 95 % of patients in the 200 mg tolcapone group while only 37 % of patients receiving the placebo had a reduced "wearing-off" effect ($p<0.01$).
- No significant differences were seen between the groups in total and subtotal scores for Subscales I, II, and III, although the UPDRS total score decreased more with tolcapone.
- In all, 57 patients (28 %) completed 12 months of treatment.
  20 in the placebo group (30 %)
  19 in the 100 mg tolcapone group (28 %)
  18 in the 200 mg tolcapone group (27 %)
- The reductions in L-dopa dosage and "off-time" seen at the end of 3 months were maintained throughout treatment in the tolcapone treated patients even though the study design allowed an increase in L-dopa dosage above the baseline dose after month 3.
- The most frequent events not related to L-dopa were diarrhoea and constipation.
- Adverse events occurred in 5 % more tolcapone treated patients than placebo treated patients.
- Tolcapone treatment was associated with raised aspartate alanine aminotransferase concentrations in 3 patients in the 100 mg tolcapone group and 2 in 200 mg tolcapone group. One of the patient was withdrawn from the study as a result.

Conclusion:

- This long term study confirms the findings of previous short term studies (Davis et al. 1995, Limousin et al. 1995, Kurth et al. 1997).
- Incidence of nondopaminergic adverse events was low, and only diarrhoea caused withdrawal, which was higher in the tolcapone group than in the placebo group.
- Nausea, dyskinesia and diarrhoea occurred only early in the study; no new incidence of these occurred after 3 months.

Appendix 3

Unified Parkinson's Disease Rating Scale (UPDRS) I-III

Subscale I: Mental activity, Behaviour, and Mood
Rate items by interview
Acceptable responses are: 0, 1, 2, 3, 4

1. INTELECTUAL IMPAIRMENT:

0 = Normal
1 = Mild; consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty having complex problems; mild but definite impairment of function at home, with need of occasional prompting.
3 = Severe memory loss, with disorientation for time and often for place.
4 = Severe memory loss with orientation preserved to person only; unable to make judgements or solve problems; require much help with personal care; cannot be left alone at all.

2. THOUGHT DISORDER

0 = None
1 = Vivid dreaming
2 = "Benign" hallucinations with insight retained
3 = Occasional to frequent hallucinations or delusions without insight; could interfere with daily activities
4 = Persistent hallucinations, delusions, or florid psychosis; not able to care for self

3. DEPRESSION

0 = Not present
1 = Periods of sadness or guilt greater than normal but never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. MOTIVATION / INITIATIVE:

0 = Normal
1 = Less assertive or disinterest in elective (non routine) activities.
2 = Loss of initiative or disinterest in elective (non routine) activities.

3 = Loss of initiative or disinterest in day-to-day (routine) activities.
4 = Withdrawn; complete loss of motivation.

Unified Parkinson's Disease Rating Scale (UPDRS) I-III

Subscale II: Activities of Daily living for ON
Rate items by interview
Acceptable responses are: 0, 1, 2, 3, 4

5. SPEECH

0 = Normal
1 = Mildly affected; no difficulty being understood
2 = Moderately affected; sometimes asked to repeat statements.
3 = Severely affected; frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. SALIVATION

0 = Normal
1 = Slight but definite excess saliva; may have night-time drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva; some drooling.
4 = Marked drooling; requires constant use of tissue or handkerchief.

7. SWALLOWING

0 = Normal
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires nasogastric tube or gastrostomy feeding.

8. HANDWRITING

0 = Normal
1 = slightly slow or normal.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = Majority of words are not legible.

9. CUTTING FOOD AND HANDLING UTENSILS

0 = Normal
1 = Somewhat slow clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must cut by someone, but can still feed slowly
4 = Needs to be fed.

10. DRESSING

0 = Normal
1 = Somewhat slow, but no help needed.
2 = Occasional assistance needed with buttoning, getting arms into sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. HYGIENE

0 = Normal
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Needs Foley catheter or other mechanical aids.

12. TURNING IN BED AND ADJUSTING BEDCLOTHES

0 = Normal
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate attempt, but cannot turn or adjust sheet alone.
4 = Helpless.

13. FALLING (unrelated to freezing)

0 = None
1 = Rare falling.
2 = Occasionally falls, less than once daily.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. FREEZING WHEN WALKING

0 = None
1 = Rare freezing when walking; may have start hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing; occasionally falls because of freezing.
4 = Frequently falls because of freezing.

15. WALKING

0 = Normal
1 = Mild difficulty; may not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking; requires assistance.
4 = Cannot walk at all, even with assistance.

16. TREMOR

0 = Absent
1 = Slight and infrequently present, not bothersome to patient.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. SENSORY COMPLAINTS RELATED TO PARKINSONISM

0 = None
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching, not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

Unified Parkinson's Disease Rating Scale (UPDRS) I-III

Subscale III: Motor Examination
Rate items by interview
Acceptable responses are: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0

18. SPEECH

0 = Normal
1 = Slight loss of expression, diction and / or volume.
2 = Monotone, slurred but understandable, moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. FACIALEXPRESSION

0 = Normal
1 = Minimal hypomimia; could be normal poker face.
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed face, with severe or complete loss of facial expression; lips parted ¼ inch or more.

20. TREMOR AT REST

0 = Absent
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent, or moderate in amplitude but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. ACTION OR POSTURAL TREMOR OF HANDS

0 = Absent
1 = Slight; present with action.
2 = Moderate in amplitude; present with action.
3 = Moderate in amplitude; present with posture-holding as well as with action.
4 = Marked in amplitude; interferes with feeding.

22. RIGIDITY (judged on passive movement of major joints with patient relaxed in sitting position; "cogwheeling" to be ignored):

0 = Absent
1 = Slight or detectable only when activated by a mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe; range of motion achieved with difficulty.

23. FINGER TAPS (patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately):

0 = Normal (≥15/5 sec)
1 = Mild slowing and /or reduction in amplitude (11 – 14/5 sec).
2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement (7 – 10/5 sec).
3 = Severely impaired; frequent hesitation initiating movements or arrests in ongoing movement (3-6/ 5 sec).
4 = Can barely perform the task (0-2/5 sec).

24. HAND MOVEMENTS (patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately)

0 = None
1 = Mild slowing and / or reduction in amplitude.
2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. RAPID ALTERNATING MOVEMENTS OF THE HANDS (pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously)

0 = Normal
1 = Mild slowing and / or reduction in amplitude.
2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. LEG AGILITY (patient taps heel on ground in rapid succession, picking up entire leg; amplitude should be about 3 inches)

0 = Normal
1 = Mild slowing and / or reduction in amplitude.
2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement.
3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. ARISING FROM CHAIR (patient attempts to arise from a straight-backed wood or metal chair, with arms folded across chest)

0 = Normal
1 = Slow, or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 =Unable to arise without help.

28. POSTURE

0 = Normal erect
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion, with extreme abnormality of posture.

29. GAIT

0 = Normal
1 = Walks slowly; may shuffle with short steps; but no festination or propulsion.
2 = Walks with difficulty but requires little or no assistance; may have some festination, short steps or propulsion.
3 = Severe disturbance of gait; requires assistance.
4 = Cannot walk at all, even with assistance.

30. POSTURAL STABILITY (response to sudden posterior displacement produced by pull on shoulders while patient is erect, with eyes open and feet slightly apart; patient is prepared)

0 = Normal
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable; tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. BODY BRADYKINESIA AND HYPOKINESIA (combining slowness, hesitancy, decreased arm swing, small amplitude and poverty of movement in general)

0 = None
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons; possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement that is definitely abnormal; alternatively, some reduced amplitude of movement.
3 = Moderate slowness; poverty or small amplitude of movement.
4 = Marked slowness; poverty or small amplitude of movement.

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