β-adrenoreceptors and the risk of Parkinson's disease

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Summary

Background β-adrenoceptors are widely expressed in different human organs, mediate important body functions and are targeted by medications for various diseases (such as coronary heart disease and heart attack) and many β-adrenoceptor acting drugs are listed on the WHO Model List of Essential Medicines. β-adrenoceptor antagonists are used by billions of patients with neurological disorders, primarily for the treatment of migraine and action tremor (mainly essential tremor), worldwide.

Recent developments An observational study reported a link between the chronic use of the β-adrenoceptor antagonist propranolol and an increased risk of Parkinson's disease, while the chronic use of the β-adrenoceptor agonists was associated with a decreased risk. Further support of this association was provided by a dose-dependent decrease in the risk of Parkinson's disease with chronic β-adrenoceptor agonist (eg, salbutamol) use, and by functional data indicating a possible underlying molecular mechanism. Five additional epidemiological studies have examined the modulation of the risk of Parkinson's disease as a result of the use of β-adrenoceptor-acting drugs in different populations. Overall, similar estimates but different interpretations of the associations were provided. Several findings suggest that the increase in risk of Parkinson's disease associated with β-adrenoceptor antagonists use can be explained by reverse causation because prodromal Parkinson's disease is often associated with non-specific action tremor, which is usually treated with propranolol. The lower risk of Parkinson's disease seen in patients receiving β-adrenoceptor agonists is likely to be indirectly mediated by smoking because smoking has a strong inverse association with Parkinson's disease (people that smoke have a reduced risk of developing Parkinson's disease). Smoking also causes chronic obstructive pulmonary disease, which is treated with β-adrenoceptor-agonist medications. Even if causal, the effect of β-adrenoceptor antagonists on the risk of Parkinson's disease would be small compared with other Parkinson's disease risk factors and would be similar to the risk evoked by pesticide exposure. The estimated risk of Parkinson's disease because of β-adrenoceptor antagonists use corresponds to one case in 10 000 patients after 5 years of propranolol use, and would be considered a very rare adverse effect. Thus, not using β-adrenoceptor antagonists would severely harm patients with recommended indications, such as heart disease or migraine. Similarly, 50 000 people would have to be treated for 5 years with salbutamol to prevent Parkinson's disease in one patient, suggesting that primary preventive therapy studies on disease modification are not warranted.

Where next? Epidemiological evidence for a causal relationship between use of β2-adrenoceptor antagonists and the increased risk of Parkinson's disease is weak, with other explanations for the association being more probable. Future observational studies are warranted to clarify this association. However, given the very low risk associated with propranolol, most clinicians are unlikely to change their treatment approach.

Introduction

Parkinson's disease is the fastest growing neurodegenerative disease, with a worldwide increase in the number of patients with the disease from 2·5 million in 1990 to 6·1 million in 2016.[1] An ageing society is the main reason for this substantial increase, but declining smoking rates, increasing industrialisation, and additional unknown factors could also contribute.[2] The prevention of Parkinson's disease has long been recognised as the best strategy to fight this development.[3,4] The International Parkinson and Movement Disorder Society developed a proposal to assess Parkinson's disease risk[5] based on the age-specific likelihood for Parkinson's disease calculated using a Bayesian classification algorithm including specific risk or protective factors. Since then, the risk factors for Parkinson's disease have been regularly updated to improve the precision of this proposed tool.[6,7]

Of the factors that could modulate the risk of Parkinson's disease, β-adrenoceptors have become a possible target.[8–15] Because β-acting agents have a major role in global health care, in this Rapid Review we summarise the observational studies examining the effect of β-adrenoceptors on Parkinson's disease risk and discuss how these new findings might affect the clinical use of these drugs.

Proposed regulation of α-synuclein expression by β2-adrenoceptor agonists and antagonists

α-Synuclein is the main constituent of Lewy bodies,[16] the pathological hallmark of Parkinson's disease in the brain.[17] With increasing disease severity, Lewy bodies and pathological α-synuclein production increase in the brain, from the vagal nucleus to the cortex, in a consistent pattern leading to the Braak pathological staging of Parkinson's disease.[18] Therefore, much research focuses on α-synuclein metabolism, in particular on drugs affecting α-synuclein concentrations. A human cell model (SK-N-MC neuroblastoma cells) showed that selective β-adrenoceptor agonists (orciprenaline, clenbuterol, and

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salbutamol) or transient transfection with the *ADRB2* gene reduced the abundance of *SNCA* mRNA encoding α-synuclein.[10] Treatment with the β-adrenoceptor antagonist propranolol or silencing of the *ADRB2* gene led to a significant (p=0·01) increase in *SNCA* mRNA and elevated α-synuclein protein concentrations.[10] The effects of β-adrenoceptor agonism on α-synuclein expression were confirmed in a study of rat primary cortical neurons and human iPSC-derived neurons in vitro[10] and in a study of the rat substantia nigra in vivo.[10] β-adrenoceptor ligands were hypothesised to modulate acetylation of lys 27 of histone H3.[10,19] This action would, in turn, regulate promoters and enhancers at *SNCA*, affecting α-synuclein transcription. Since a chronic increase in α-synuclein expression, induced for example by *SNCA* gene duplication or triplication, is known to be sufficient to cause α-synuclein aggregation and the pathological hallmarks and symptoms of Parkinson's disease,[20] the authors proposed that chronic use of the β-adrenoceptor antagonist propranolol might facilitate the development of Parkinson's disease, and that β-adrenoceptor agonists might constitute a possible preventive strategy in Parkinson's disease.

Biological and clinical role of β blockers

Biological function of the β-adrenoceptors

β-adrenoceptors are a family of G-protein-coupled receptors. β1-adrenoceptors are mainly expressed in cardiac tissue and the CNS, β2-adrenoceptors are expressed in bronchial and blood vessel smooth muscle cells, and β3-adrenoceptors are expressed mainly in the bladder and in adipose tissue, where they primarily regulate relaxation of the bladder and lipolysis. In the heart, blockage of β1-adrenoceptors (eg, by use of β1-selective or non-selective β-adrenoceptor antagonists) decreases heart rate and contractility, thereby reducing cardiac output. In the bronchial smooth muscles, stimulation of β-adrenoceptors (eg, with inhaled β-adrenoceptor agonists) leads to bronchodilation. β1 and β2-adrenoceptors are expressed in the brain.[21] However, their brain receptor function is still poorly understood; central β2-adrenoceptor blockade is assumed to have beneficial effects on tremor.[22] Changes to β-adrenoceptor function and loss of β-adrenoceptors with age might be involved in age-related changes in arousal, mood, and memory.[23] Furthermore, β-adrenoceptors have a role in modulating migraine and stress.[24,25]

β-adrenoceptor agonists and antagonists: clinical use, benefits, and side-effects

Both β-adrenoceptor agonists and antagonists, initially developed in the 1960s, have routinely been used in clinical practice for decades. β-adrenoceptor agonists constitute the frontline treatment for asthma and chronic obstructive pulmonary disease, reducing mortality worldwide.[26,27] β-adrenoceptor antagonists are widely used to treat common diseases, including arterial hypertension, ischaemic heart disease, heart failure, tachyarrhythmia, migraine, and tremor.[22,28,29] Ischaemic heart disease is the leading cause of total years of life lost.[30] Approximately 423 million people worldwide have cardiovascular disease, from which 18 million die every year.[30–32] β-adrenoceptor antagonists have substantially beneficial effects on cardiovascular mortality.[33,34] In the three largest efficacy trials of β-adrenoceptor antagonists in patients with heart insufficiency, β-adrenoceptor antagonists reduced the all-cause mortality risk by approximately 34%, all-cause hospitalisation risk by around 20%, and risk of sudden death by about 40%.[35–37]

Migraine and essential tremor are two of the most common neurological diseases.[1,38] WHO lists the β-adrenoceptor antagonist propranolol for migraine prophylaxis on their Model List of Essential Medicines (EML).[39] The 2016 Global Burden of Disease, Injuries, and Risk Factors Study estimates that 1·04 billion people worldwide have migraine.[40] Assuming the world population to be 7·64 billion and the worldwide prevalence of essential tremor to be 0·9% in 2019,[38] 69 million patients are estimated to have essential tremor, for which propranolol is the first-line treatment. For these disorders, the disease burden is not premature death, but reduced quality of life—measured as years lived with disability. For migraine, for example, years lived with disability was estimated to be 45·1 million years worldwide, in 2016,[40] which is 2% of all disability-adjusted life years worldwide.

On a population-basis, severe side-effects (which are diverse but can include liver and kidney damage) of β-adrenoceptor agonists and antagonists are infrequent. The benefits of β-adrenoceptor agonists and antagonists outweigh the low risk of the mild-to-moderate side-effects associated with these drugs, which are listed as essential medicines on the WHO Model List of Essential Medicines.[39]

β blockers as a risk factor for Parkinson's disease

Epidemiological evidence of risk modulation with β-adrenoceptor acting drugs

Several observational studies have addressed the potential relationships between commonly used drugs (eg, ibuprofen) and Parkinson's disease risk, investigating a hypothetical neuroprotective drug effect.[3,14,41–43] However, the results of these studies are contradictory.

Six studies[10–15] have evaluated the risk-modulating effect of β2-adrenoreceptor-acting drugs (figure 1A). β-adrenoceptor antagonists (eg, propranolol) were associated with an increased risk of Parkinson's disease (rate ratio [RR] 2·20, 95% CI 1·62–3·00) in an observational Norwegian cohort study (figure 1A).[10] Furthermore, a dose-dependent decrease in Parkinson's disease risk was seen in people using the β-adrenoceptor agonist salbutamol (RR 0·66, 0·58–0·76).[10] Inhaled corticosteroids showed no association with the risk of Parkinson's disease after adjustment for salbutamol use and level of education.[10] However, this study did not provide data on other β-adrenoceptor antagonists (excluding propranolol), did

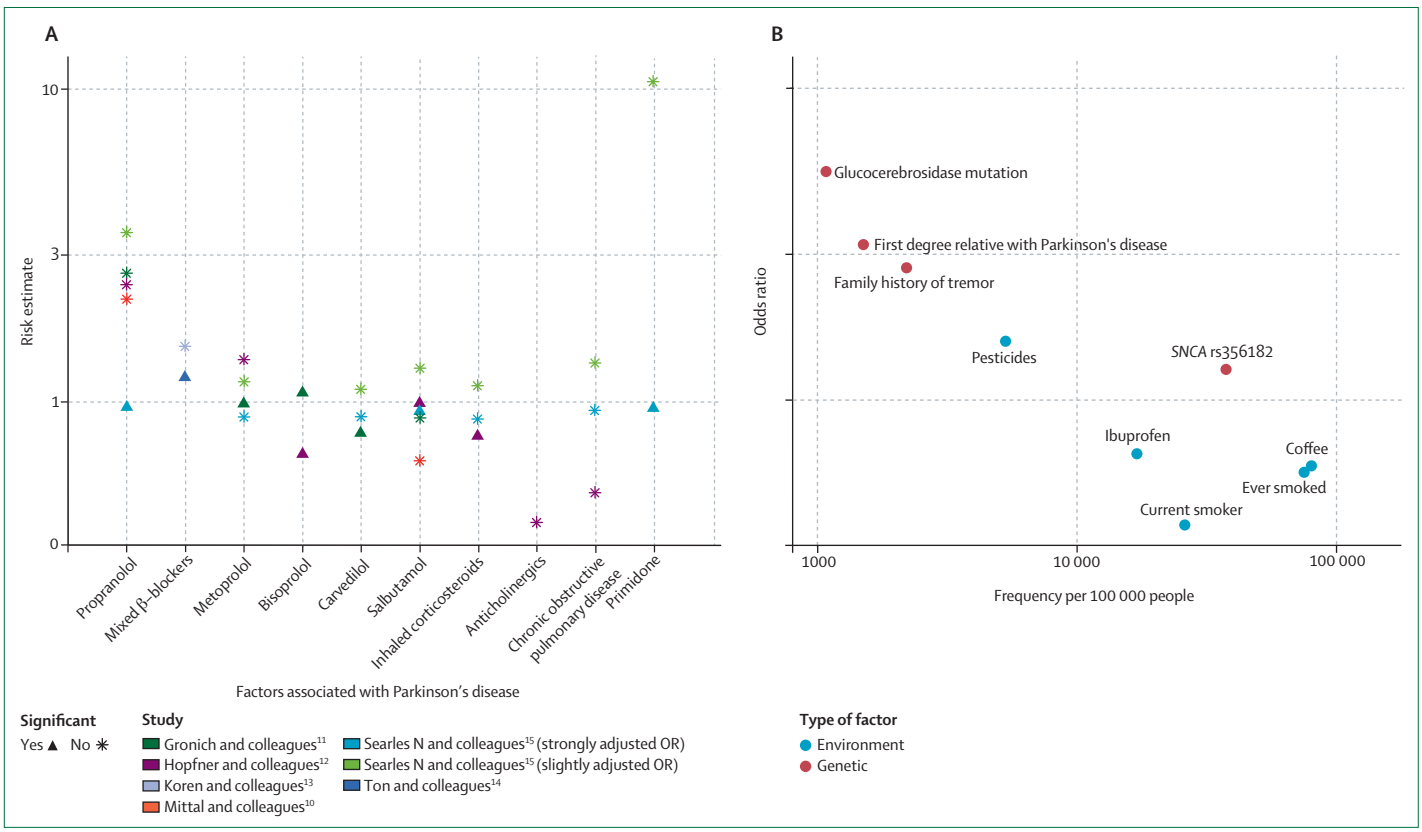

Figure 1: **Factors associated with Parkinson's disease**
A) Risk estimates for Parkinson's disease reported for β-adrenoreceptor antagonists and agonists in six different studies: Mittal and colleagues[10] (rate ratio), Gronich and colleagues[11] (rate ratio), Hopfner and colleagues[12] (odds ratio), Koren and colleagues[13] (hazard ratio), Ton and colleagues[14] (odds ratio), and Searles-Nielsen and colleagues[15] (slightly adjusted odds ratio; strongly adjusted odds ratio). B) Known factors considered to modify the risk of Parkinson's disease.[7,43-45] The x-axis shows their approximate frequency in the population. Risk estimate values higher or lower than 1 indicate increased or reduced risk compared with the general population.

not adjust for smoking, and included level of education as a crude proxy for smoking.[10] Furthermore, only individuals with cardiovascular diseases were included and those with neurological indications for propranolol were excluded.[10] In summary, the association between β-adrenoceptor antagonists and Parkinson's disease was interpreted as causal in this study.

In an Israeli study, based on the Clalit Health Services database, the risk of Parkinson's disease (defined by International Classification of Diseases [ICD] coding) increased with the use of the β-adrenoceptor antagonist propranolol (RR 2·6, 95% CI 2·40–2·81) and decreased with the use of the β-adrenoceptor agonists (RR 0·89, 0·82–0·96).[11] The risk for Parkinson's disease increased in a dose-dependent manner with increasing use of β-adrenoceptor antagonists, although this was only observed for propranolol, with no data reported for other β-adrenoceptor antagonists. Furthermore, the risk of Parkinson's disease decreased with increasing use of β-adrenoceptor agonists. Additionally, the effect sizes observed were generally numerically larger for long-acting (approximately 12 h) and ultralong-acting (approximately 24 h) compared with short-acting (approximately 4–6 h) β-adrenoceptor agonists. These results showing an increased risk of Parkinson's disease withstood exclusion of all individuals in which a diagnosis of essential tremor was recorded before the later diagnosis of Parkinson's disease. However, the effect of adjustment and how smoking and chronic obstructive pulmonary disease (and ideally other chronic obstructive pulmonary disease drugs) were associated with Parkinson's disease was not possible to delineate because only adjusted estimates were provided (figure 1A).[11] Thus, the data do not allow the exclusion of a possible indirect association of β2-adrenoceptor agonists with Parkinson's disease risk mediated via chronic nicotine use.

Another study from Israel used electronic medical records from the Maccabi Health Services database to assess the risk of β-adrenoceptor antagonists use and the development of Parkinson's disease.[13] Smoking status was obtained from the patient's record and considered for matching; however, the matching procedure and final sample size were inconsistently reported, and no information on essential tremor status has been provided. The hazard ratio (HR) associating the use of any β-adrenoceptor antagonists with the risk of Parkinson's disease

was 1·51 (95% CI 1·28–1·77), with effects observed even at very low exposure to β-adrenoceptor antagonists.[13] The association between Parkinson's disease and β-adrenoceptor agonists use was not assessed. This study showed an association between β-adrenoceptor antagonists and the risk of Parkinson's disease.

A study[15] from the USA, based on Medicare data,[46] found that propranolol, but not other β-adrenoceptor antagonists, increased the risk of Parkinson's disease (defined by ICD coding) in unadjusted analyses (figure 1A) with an odds ratio (OR) of 3·62 (95% CI 3·31–3·96). However, the association between the risk of Parkinson's disease and propranolol use was abolished when adjusting for tremor (defined by ICD coding) reported before the diagnosis of Parkinson's disease (adjusted OR 0·97, 0·80–1·18).[15] In this study, a validated smoking variable was included in the models to adjust for confounding. Of all the epidemiological studies included in this Rapid Review, this study[15] provides the most comprehensive adjustment for potential confounders because it adjusted for demographics, smoking, and overall use of medical care. As such, the ORs in this study[15] can only be compared with other studies under certain conditions.[10–14] As for β-adrenoceptor agonists,[16] the OR associating salbutamol with the risk of Parkinson's disease was close to one after adjustment for smoking (adjusted OR 0·97, 0·93–1·01; figure 1A).[15] No dose-response association with Parkinson's disease risk was seen in salbutamol users.[15] Additionally, a strong positive association was reported between the risk of Parkinson's disease and the use of primidone, a non-β2 adrenoreceptor-active antitremor medication for action tremor.[15] The association with propranolol (OR 9·68, 8·35–11·2; figure 1A) attenuated with either adjustment for tremor or with exposure lagging (OR 0·96, 0·68–1·36).

Another study from the USA, published before the findings of a potential molecular effect of β-adrenoceptor antagonists and agonists on Parkinson's disease risk were reported,[14] investigated the risk of Parkinson's disease associated with β-adrenoceptor antagonists in a population-based case-control study of Parkinson's disease.[14] No association was found between the risk of Parkinson's disease and use of β-adrenoceptor antagonists with an adjusted OR (ever use) of 1·20 (95% CI 0·71–2·03) for β-adrenoceptor antagonists.[14] Furthermore, no association was found between Parkinson's disease risk and duration, dose, number of prescriptions, or drug regimen of β-adrenoceptor antagonist use.[14] When only patients were included who used metoprolol and propranolol the risk estimate for ever having used β blockers increased, but remained non-significant (OR 1·47, 95% CI 0·80–2·69). However, for these drugs, smaller associations were seen with longer-term compared with shorter-term use, which contradicts our understanding of Parkinson's as a slow neurodegenerative disorder.

In a Danish case-control study, only the β-adrenoceptor antagonists propranolol and metoprolol were found to be associated with an increased risk of developing Parkinson's disease (defined by ICD coding).[12] These associations were stronger for short-term (<1 year; OR 1·97, 95% CI 1·70–2·28) compared with long-term drug use (>3 years; OR 1·28, 1·10–1·47). Long-term (>3 years) β-adrenoceptor agonist use, however, was associated with reduced risk of Parkinson's disease (OR 0·57, 0·40–0·82; figure 1A),[12] while short-term (<1 year) agonist use also showed a reduced risk of developing Parkinson's disease (OR 0·69, 0·57–0·82). Furthermore, the reduced risk of developing Parkinson's disease was not specific to β-adrenoceptor agonists: it was also found for other drugs prescribed for chronic obstructive pulmonary disease (which is associated with chronic smoking), in particular inhaled anticholinergics (OR 0·42, 0·25–0·67) and inhaled steroids (OR 0·78; 0·59–1·02).[12] This study does not provide data on smoking so that an adjustment for markers of smoking was performed. The study confirmed β2-adrenoceptor agonist use to be associated with reduced risk of developing Parkinson's disease and β2-adrenoceptor antagonist use with increased risk of developing Parkinson's disease risk.

In observational studies investigating comorbidities and medications in patients with Parkinson's disease, β-adrenoceptor antagonists have also been associated with an increased risk of Parkinson's disease.[7] By contrast, the association between β-adrenoceptor agonists and antagonists with the risk of developing Parkinson's disease had not been discovered at the population level for decades or in any previous large prospective cohort studies, such as the Rotterdam,[47] Honolulu-Asia Ageing,[48] and Shanghai Women Health studies,[49] although the medication had been systematically documented within these studies.

To provide a better context for interpretation, we have compared the magnitude of the association between the risk of Parkinson's disease and β-adrenoceptor antagonist use with other known risk factors for the development of the disease (figure 1B). Under the assumption of a causal association between β-adrenoceptor antagonist use and the risk of Parkinson's disease, the OR for Parkinson's disease after 11 years of propranolol use (OR 2·20, 95% CI 1·62–3·00)[10] was similar to the OR of an individual with a family history of tremor (OR 2·74, 2·10–3·57)[7] or a first-degree relative with Parkinson's disease (OR 3·23, 2·65–3·93).[7] The risk evoked by any previous exposure to pesticides (OR 1·62, 1·4–1·88)[43] is similar to that evoked by the strongest common genetic variant associated with Parkinson's disease (rs356182 in *SNCA*; OR 1·34, 95% CI 1·30–1·36, per effect allele; figure 1B).[44] Carrying any glucocerebrosidase mutation leads to a substantial increase in the risk of Parkinson's disease (OR 5·43, 3·89–7·57) across different populations (figure 1B).[45]

Interpretation of the epidemiological evidence

Six studies have examined the link between the risk of developing Parkinson's disease and the use of β-adrenoceptor agonists and antagonists.[10,11–15] Data on the risk of developing Parkinson's disease with β-adrenoceptor antagonists or

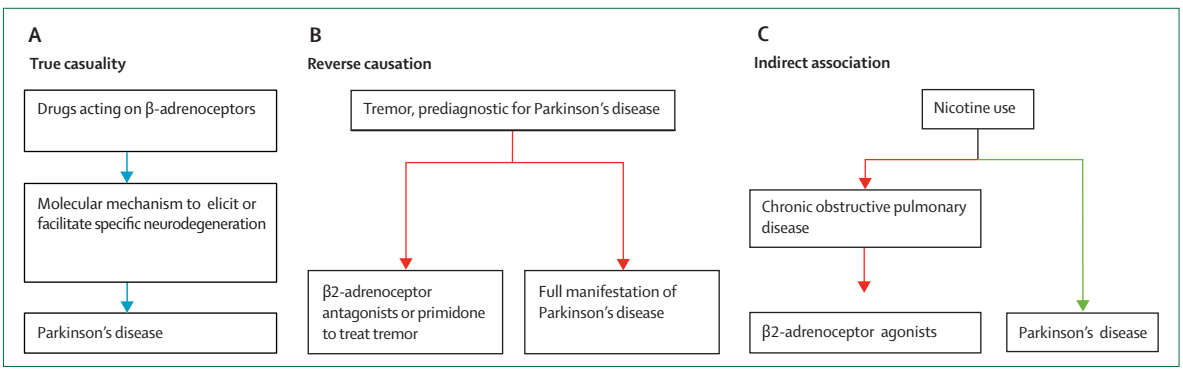

Figure 2: **Possible concepts explaining the epidemiological association of β-adrenoceptor agonists and antagonists with the risk of developing Parkinson's disease**
Blue arrows show bidirectional (preventive or provoking) effects, red arrows represent provoking effects, green arrows show preventive effects. A) A causal relationship has been proposed between β-adrenoreceptor agonists and antagonists use and the risk of Parkinson's disease by bidirectional modulation of the expression of *SNCA* mRNA and α-synuclein protein via β-adrenoreceptors, which would affect α-synuclein aggregation as a key element in the pathogenesis of Parkinson's disease.[10] B) Reverse causation might explain the association between β-adrenoreceptor antagonists and the risk of Parkinson's disease because tremor is often treated with β-adrenoreceptor antagonists and can preceed the onset of other Parkinsonian signs and thus the diagnosis of fully manifest Parkinson's disease. In that scenario, Parkinson's disease-associated tremor would cause the use of β-adrenoceptor antagonists. C) An indirect association of β-adrenoceptor agonists use with the reduced risk of Parkinson's disease might be apparent by the linking factor of chronic nicotine use. Smoking is the most frequent cause of chronic obstructive pulmonary disease, most commonly treated with β-adrenoreceptor agonists. Independent of this effect, smoking is also known to be associated with a reduced risk for Parkinson's disease.[50]

agonists use can be interpreted as true causality (figure 2A),[10] reverse causation (figure 2B), or indirect association (figure 2C).[15]

True causality (figure 2A) would assume that Parkinson's diesease risk is indeed increased or decreased by exposure to β-adrenoceptor antagonists or agonists. The reverse causation hypothesis (figure 2B) assumes that patients are prescribed propranolol because of tremor as an initial manifestation of Parkinson's disease, preceding the onset of other Parkinsonian symptoms including bradykinesia and rigidity. Tremor has been shown to precede Parkinson's disease diagnosis in some patients by up to 7 years.[7,51] During this very early period of Parkinson's disease, tremors are often unspecific action tremors, which are sometimes misinterpreted as essential tremor.[52] Unspecific action tremors are treated with the β-adrenoceptor antagonist propranolol and the antagonist primidone.[22] Reverse causation is suggested by one study,[15] which shows that the risk of developing Parkinson's disease decreased to null when the model was adjusted by the essential tremor diagnosis or by medication with primidone.[15] Furthermore, tremor is more frequent closer to Parkinson's disease diagnosis; therefore, disease risk estimates are expected to increase specifically for short-term use of β-adrenoceptor antagonists, as was observed in several of the studies.[11,12,15] Finally, with the exception of metoprolol, other β-adrenoceptor antagonists, not used to treat action tremor, do not increase the risk of Parkinson's disease.[11,12,15]

For β-adrenoceptor agonists, an indirect association (figure 2C) has been suggested on the basis of smoking acting as the relevant and uncontrolled confounder. Patients who smoke have a decreased risk of developing Parkinson's disease,[7,46] but they develop chronic obstructive pulmonary disease that is subsequently treated with β-adrenoceptor agonists, which might explain why they are indirectly associated with a reduced risk of Parkinson's disease, with chronic nicotin use being the causal link. The protective effect of smoking is strong. For example, a large meta-analysis[50] including 44 case-control studies and four follow-up studies studies reported a pooled relative risk of Parkinson's disease of 0·59 (95% CI 0·54–0·63) for former smokers and 0·39 (0·32–0·47) for current smokers. Although slightly smaller than that seen by smoking, the mean reduction in Parkinson's disease risk by salbutamol (mean OR 0·87) is in the order of the overall presumed risk reduction induced by smoking (figures 1A, B).[7,43,53] In one study,[15] the effect of salbutamol (OR 1·29, 1·25–1·33) was completely abolished by adjustment for smoking (OR 0·97, 0·93–1·01), which again suggests that smoking mediates the association between drug use and the development of Parkinson's disease (figure 1B). In the Israeli study[11] based on the Clalit Health Services database, in which all risk estimates were adjusted for smoking, salbutamol was still associated with a reduced risk of Parkinson's disease (RR 0·89, 0·82–0·96). Other drugs, such as inhaled steroids and anticholinergics, to treat chronic obstructive pulmonary disease, were also associated with a decreased risk of Parkinson's disease,[12,15] despite that no biological mechanism for protection against Parkinson's disease has been proposed for these drugs. Hence, indirect association is the most likely mechanism for the association between the risk of developing Parkinson's disease and the use of β-adrenoceptor agonists.

Making informed decisions

Clinicians must routinely decide whether to prescribe β-acting drugs, and they should be aware of the risks and benefits associated with their use. In our view, changing the beneficial and extensive use of β-adrenoceptor-acting

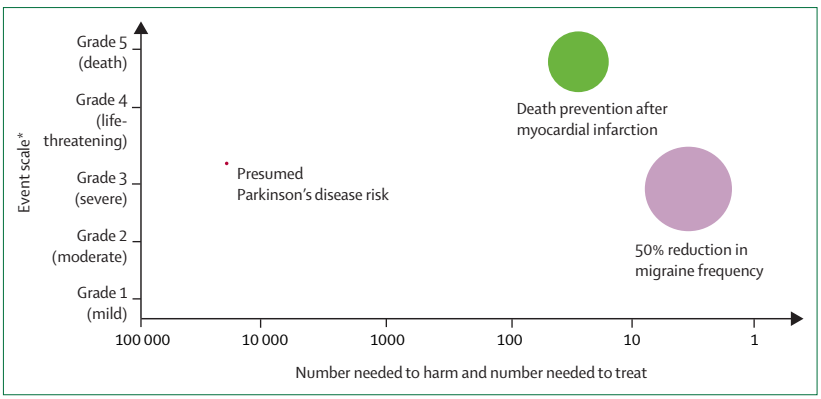

Figure 3: **Risk-benefit evaluation of β-adrenoceptor antagonists**
*Event scale based on the grading of adverse events according to the Common Terminology Criteria for Adverse Events scale implemented by the National Institute of Health and the National Cancer Institute, USA.[55] The red circle indicates the presumed risk of Parkinson's disease evoked by β2-adrenoreceptor antagonists. Mittal and colleagues[10] suggest that 28 571 individuals have to be treated for 5 years with propranolol to provoke Parkinson's disease in one patient. The green circle represents death prevention after myocardial infarction using β-adrenoreceptor antagonists. 42 patients need to be treated with β-blockers for 2 years to prevent one death after infarction.[29] The purple circle indicates a 50% reduction in migraine frequency (severity of event) upon treatment with β-adrenoreceptor antagonists.[56] The area of each circle is proportional to the frequency of the respective event.

drugs cannot be based on possible molecular effects in a cell model. However, strong epidemiological evidence (eg, increased blood pressure as a risk factor for stroke) has always been a reasonable guide for clinical decision making. From the data reported in a Norwegian study,[10] the number needed to harm was calculated as

$$\frac{1}{\text{Event rate in control group} - \text{Event rate in propranolol group}}$$

These data, reported by Mittal and colleagues[10] suggested that, under the assumption that the observed association is causal, 28 571 individuals have to be treated for 5 years with propranolol for one patient to develop Parkinson's disease. After 11 years of propranolol treatment, one case of Parkinson's disease might statistically occur in a group of 559 individuals,[10] with similarly low number needed to harm in the other five studies.[11–15] However, the stronger effect for longer (11 year follow-up) treatment periods compared with short-term treatment periods (5 year follow-up) could not be reproduced in two studies.[12,15] The development of Parkinson's disease is considered a very rare adverse drug reaction at 5 years (incidence <1 case per 10 000 patients), and the risk of developing Parkinson's disease after 11 years of propranolol use would be considered as uncommon or infrequent (ranging from an incidence of 1 case per 1000 to 1 case per 100 patients) according to the Council of International Organizations of Medical Sciences.[54] Thus, we conclude that even under the assumption of causality, the increase in the risk for Parkinson's disease is small, albeit in the order of pesticide-associated risk (figure 1B).

By contrast, there is robust evidence of the beneficial effects of propranolol in defined diseases. For example, for heart disease, the number needed to treat over 2 years to avoid one death with β blockers after heart infarction has been estimated to be 42 patients.[29] Here, the risk-benefit assessment is in favour of the use of propranolol (figure 3).[57] Avoiding the use of β-adrenoceptor antagonists for fear of Parkinson's disease could be considered as unethical given the strong effects on mortality. Propranolol is the world's most widely-used treatment for heart disease, on which its positive effects are best reported. However, the benefit-risk balance is different for non-life-threatening illnesses, such as migraine and essential tremor. In a dose-dependent manner, on average the use of propranolol leads to a 44% reduction in migraine activity.[58] In a Cochrane analysis, placebo-controlled trials reported the RR of responding to propranolol treatment to be 1·94 (1·61–2·35).[59] Despite the methodological limitations in a majority of the available trials, there is robust evidence that propranolol is superior to placebo in the treatment of patients with migraine. For essential tremor, propranolol and primidone are the drugs of choice.[22] In a dose-dependent manner, there is a tremor reduction of 50% in about 75% of patients.[60,61] In both diseases, guidelines[22,58–61] recommend starting treatment according to the symptom severity, which can be already initatied in young adulthood, resulting in long-term treatment. Thus, the prevalence of Parkinson's disease should be higher in patients with essential tremor, which is controversial due to conflicting reports.[62,63] Certain tremor syndromes, such as age-related postural tremor syndromes, represent as transitional conditions, some of which develop into Parkinson's disease.[64] These studies show that β blockers are helping millions of patients. Restriction of propranolol use would put important progress of modern medicine into question. Alternative medications for migraine prevention and essential tremor are, unlike propranolol, not available in many countries.[65]

Even if a possible risk-reducing potential of salbutamol exists, this effect is unlikely to justify preventive treatment with a β-adrenoceptor agonist because of its small overall public health effect: therapeutic salbutamol intake for 5 years had an RR of 0·43,[10] suggesting that protection from the disease is similar to the degree of protection experienced by current smokers (RR 0·44, 95% CI 0·39–0·50; figure 1B). Based on an epidemiological study,[10] 50 000 individuals would have to be treated for 5 years with salbutamol to prevent Parkinson's disease in one patient.

Conclusions and future directions

To date, the epidemiological evidence for an increased risk of developing Parkinson's disease because of β-adrenoceptor antagonists is weak, and, from our point of view, alternative explanations are more convincing.[12,14,15] Under the questionable assumption that the association between Parkinson's disease and β-adrenoceptor antagonists represents a causal relationship, the potential risk

Search strategy and selection criteria

Articles for this Rapid Review were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles published between Jan 1, 2017, and Aug 1, 2019, using the search terms "Parkinson's disease and Beta adrenoreceptor", "Parkinson's disease and β2-adrenoreceptor", "Parkinson's disease and Beta Blocker", "Parkinson's disease and β2-adrenoreceptor antagonist", and "Parkinson's disease and β2-adrenoreceptor agonist". The final reference list was generated on the basis of novelty and relevance to this Rapid Review.

by β-adrenoceptor antagonists is similar to the risk evoked by pesticide exposure[43] and the strongest common genetic variant associated with Parkinson's disease.[44] Given the rare and low risk of developing Parkinson's disease associated with propranolol use, most clinicians are unlikely to change their treatment approach. Howver, some might choose alternative treatment options when possible given the remaining uncertainties.

Because current data argues against a causal nature of the association, future observational studies are warranted to clarify the risk-benefit profile of this important class of drugs. Future big data approaches will help to assess Parkinson's disease risk and protective factors in large population samples. Finally, clinical trials for neuroprotection are not indicated because the estimated effect size of β-adrenergic receptor agonists is too small to be of clinical relevance.

Contributors

FH, GUH, AP, GK, CK, MW, and GD contributed to the conception of the Review, data analysis, data interpretation, and writing of this Review. FH, GUH, GK, and GD designed and drafted the figures. FH, GUH, AP, GK, MW, GD, KC, and CMT contributed to the literature search, data collection, and writing of this Review.

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