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ANTIPSYCHOTIC POLYPHARMACY IN THE TREATMENT OF SCHIZOPHRENIA

– a health technology assessment

Summary

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Summary

Introduction

Schizophrenia is a psychiatric disease affecting several domains of mental functioning. The course of schizophrenia varies but often it is a chronic and disabling disease. Antipsychotic drugs are the cornerstone in the pharmacological treatment of schizophrenia.

Antipsychotic polypharmacy (concomitant treatment with more than one antipsychotic drug) is frequently used in the pharmacological treatment of schizophrenia, both in Denmark and internationally. The frequent antipsychotic co-prescribing does not comply with international and national evidence-based clinical guidelines, which recommend that antipsychotic monotherapy (treatment with only one antipsychotic drug at a time) should be the preferred treatment regimen.

Objective

The aim of this health technology assessment is to explore how antipsychotic polypharmacy may be reduced by intervention methods and organisational changes.

Target group

The report is directed at decision-makers at the level of the management board of regions and mental health centres.

Delimitation

This report only discusses antipsychotic polypharmacy in the context of schizophrenia spectrum disorders, because the principles of treatment regarding other psychiatric disorders, e.g. bipolar affective disorder, differ substantially.

Methods

The contents of this report are based upon literature studies concerning the relevant health technology assessment questions and specific national studies conducted in relation to the preparation of the report: 1) a questionnaire survey investigating geographic variation in prescribing practice and associated factors, 2) an educational intervention study aiming to reduce the prevalence of antipsychotic polypharmacy, and 3) an economic study evaluating the costs of health care services associated with antipsychotic polypharmacy and monotherapy, respectively.

Technology

The prevalence of antipsychotic polypharmacy is high and steadily rising. This treatment regimen is used in approximately half of all Danish outpatients with schizophrenia, but with substantial geographic variation.

Overall there is no evidence that antipsychotic polypharmacy has superior efficacy compared with antipsychotic monotherapy, except in patients resistant to antipsychotic monotherapy including clozapine (about 15 % of all patients). Only in this limited subgroup of patients there is some evidence for a small beneficial effect of clozapine combination treatment. It has been shown that antipsychotic combination treatment is

associated with an increased rate of side effects, whereas recent well-designed epidemiological studies have not found an increased risk of death associated with antipsychotic polypharmacy compared with monotherapy.

The most commonly cited arguments for antipsychotic co-prescribing include insufficient treatment response to monotherapy and attempt to reduce side effects.

The following patient characteristics have predicted antipsychotic polypharmacy in several studies: younger age, a diagnosis of schizophrenia, previous hospitalisations, male gender, long disease duration, coercion, and living alone. Contradictory findings have been reported regarding any correlation with disease severity.

Organisation

The effect of different techniques to alter physician prescribing practice and/or to implement clinical practice guidelines has been studied extensively. There is a mixture of positive and negative results and the effect size in the positive studies is small to moderate.

The following techniques have been found the most efficient: multifaceted intervention programmes (consisting of more than one element/approach), educational outreach visits, audit, feed back, educational meetings, and reminders. However, the evidence is too limited to decide which strategies might be most efficient under different circumstances.

The primary literature investigating specific methods to reduce the frequency of antipsychotic co-prescribing has reported both positive and negative results. None of the methods have shown consistent superior efficacy.

Our own educational intervention in an area of Denmark with a high frequency of antipsychotic co-prescribing did not reduce the prescribing frequency of antipsychotic polypharmacy. However, we did identify a number of organisational barriers concerning the implementation of the intervention techniques which were of potential importance and should serve as important guidance for future interventions.

Our questionnaire survey identified a number of clinician and organisation specific elements associated with the frequency of antipsychotic co-prescribing, especially attitudinal and academic elements, and elements concerning the working environment. Thus, areas with high prevalence of antipsychotic polypharmacy was associated with less frequent education and research actitvity, reduced availability of and reduced attention towards clinical practice guidelines.

The indication for antipsychotic co-prescribing is often not well documented in the medical record which makes it even more complicated to try reducing the number of drugs.

The organisational analysis was limited to elements associated with prescribing behaviour and the results should therefore be interpreted with caution.

Economics

The literature on health economic issues in this area is limited. Several studies have reported increased medication costs with antipsychotic polypharmacy compared to monotherapy, but the increase in cost has not been related to efficacy. With the assumption from the literature, that antipsychotic polypharmacy and monotherapy has equivalent efficacy, antipsychotic polypharmacy will be less cost-effective than antipsychotic monotherapy.

Our economic analysis conducted in a Danish setting showed that antipsychotic polypharmacy was associated with an increased use of health care services and as such, increased costs. However, the results should be interpreted cautiously due to the risk that it the most severely diseased, who already have a larger use of health services, who are treated with antipsychotic polypharmacy (confounding by indication). The sensitivity analysis included adjusting for GAF (Global Assessment of Functioning) score as a proxy of disease severity. The results indicated that level of functioning/disease severity was an important confounder regarding the association of antipsychotic polypharmacy with health service cost. Thus, the results indicate that antipsychotic polypharmacy is not cost-effective compared with monotherapy from the perspective of the health care system. This result adds to the list of arguments against the frequent prescribing of antipsychotic polypharmacy.

Overall evaluation

Both the literature and our own results indicate that organisational factors are essential for development and change. Therefore, it is recommended that future efforts to change prescribing practice are designed as a controlled organisational development.

Based on the literature review and our questionnaire survey specifically addressing a Danish context, it is the opinion of the project group that implementing an evidence-based treatment algorithm and prioritising education and research constitute important elements in such a development aimed at changing prescribing behaviour.

The statements in this report are based on a critical literature review and our own studies specifically addressing a Danish context. It is a considerable strength of the report to include Danish investigations because the complexity of prescribing practice makes it difficult to directly transfer results from foreign countries.

Both the questionnaire survey and the economic analysis are observational in design and therefore no causal relations can be inferred. The observed associations might have been caused by non-measured variables.

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