

แนวทางการใช้ยารักษา โรคจิตเภทที่ไม่ตอบสนองต่อการรักษา



กรมสุขภาพจิต

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และคณะทำงานเพื่อพัฒนา PTRS Guideline

- โครงการนี้เป็นกิจกรรมทางวิชาการของราชวิทยาลัยจิตแพทย์แห่งประเทศไทยและได้รับทุนอุดหนุนจากสถาบันวิจัยระบบสาธารณสุข
- ความเห็นและข้อเสนอแนะในเอกสารนี้เป็นของคณะทำงานฯ เท่านั้น มิใช่เป็นความเห็นขององค์กรทั้งสอง
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กิตติกรรมประกาศ

คณะทำงานใคร่ขอขอบคุณสถาบันวิจัยระบบสาธารณสุข โดยเฉพาะ นายแพทย์อนุวัฒน์ ศุภชุติกุล ที่ได้ให้ความเห็นที่เป็นประโยชน์อย่างยิ่งตลอดเวลาที่ทำกรพัฒนาแนวทางการรักษาฯ นี้ และคุณงามจิตต์ จันทรสาทิต ที่ได้ช่วยประสานงานจนกระทั่งการพัฒนาแนวทางการรักษาฯ นี้ สำเร็จลงได้ด้วยดี

พร้อมกันนี้ใคร่ขอขอบคุณคุณสุชาดา โชติกานนท์หัวหน้างานห้องสมุดคณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ และเจ้าหน้าที่ห้องสมุดทุกท่านที่ได้ช่วยเหลืออย่างมากในการรวบรวมบทความที่ต้องใช้ในการจัดทำแนวทางการรักษาฯ นี้

บทคัดย่อ

วัตถุประสงค์: โรคจิตเภทที่ไม่ตอบสนองต่อการรักษาเป็นปัญหาที่พบบ่อยในผู้ป่วยโรคจิตเภท ปัญหานี้ก่อให้เกิดปัญหาทางเศรษฐกิจอย่างมากต่อสังคม เนื่องจากจนถึงปัจจุบันยังไม่มีแนวทางการรักษาโรคจิตเภทที่ไม่ตอบสนอง คณะทำงานเพื่อพัฒนาแนวทางการรักษาโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาจึงเสนอที่จะพัฒนาแนวทางเวชปฏิบัติทางคลินิกที่อิงหลักฐานทางวิชาการที่เกี่ยวข้องกับการใช้ยารักษาโรคจิตเภทที่ไม่ตอบสนองต่อการรักษา

วิธีการ: คณะทำงานเพื่อพัฒนาแนวทางการรักษา ประกอบด้วยจิตแพทย์ 1 ท่าน, นักจิตวิทยา 1 ท่าน และเภสัชกร 1 ท่าน คณะทำงานได้ทำการค้นหาค้นหาบทความใน MEDLINE เพื่อหาค้นหาบทความที่เกี่ยวข้องซึ่งตีพิมพ์ในช่วงปี ค.ศ. 1966–1998 หลักฐานทางวิชาการจาก 163 บทความได้ถูกสกัดและจัดลำดับโดยอาศัยระบบที่ปรับปรุงจากระบบที่ใช้โดย Agency for Health Care Policy and Research (AHCPR) ความหนักแน่นของคำแนะนำได้ถูกแบ่งออกเป็น A, B และ C

ผลการศึกษา: สำหรับผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อยารักษาโรคจิตชนิดดั้งเดิม แพทย์ควรเปลี่ยนยารักษาโรคจิตชนิดดั้งเดิมตัวแรกเป็นยารักษาโรคจิตชนิดดั้งเดิมตัวที่สองซึ่งอยู่ในกลุ่มที่ต่างไปจากยาตัวแรก (A) ผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาที่เหมาะสมด้วยยารักษาโรคจิตอย่างน้อยสองตัวควรได้รับการวินิจฉัยว่าเป็นผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษา สำหรับผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาซึ่งกำลังได้รับยารักษาโรคจิตในขนาดสูง (อย่างน้อย 50 mg/วัน ของยา haloperidol หรือเทียบเท่า) แพทย์ควรใช้วิธีลดขนาดยาลง (B) สำหรับผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาที่กำลังได้รับยารักษาโรคจิตในขนาดปกติ แพทย์ควรคำนึงถึงการให้ยา clozapine ก่อนเป็นอันดับแรก (A) และหากผู้ป่วยไม่ตอบสนองกับยา clozapine แพทย์ควรเพิ่มยารักษาโรคจิตชนิดดั้งเดิมหนึ่งตัว โดยเฉพาะ ยา sulpiride (A) และยา loxapine (B) ยา risperidone เป็นยาที่ควรคำนึงถึงในผู้ป่วยที่ไม่ตอบสนองต่อการรักษาซึ่งปฏิเสธการตรวจเลือดอย่างสม่ำเสมอหรือมีข้อห้ามใช้ยา clozapine (A) แม้ว่าจะยังไม่หลักฐานสนับสนุนการใช้ยา olanzapine (หรือยารักษาโรคจิตชนิดผิดพวกตัวอื่นที่จะมีใช้ในอนาคต) ในผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อทั้งยารักษาโรคจิตชนิดดั้งเดิมและยา risperidone การให้ยา olanzapine (หรือยารักษาโรคจิตชนิดผิดพวกตัวอื่นที่จะมีใช้ในอนาคต) ก็อาจนำมาทดลองใช้ได้หากผู้ป่วยดังกล่าวปฏิเสธการใช้ยา clozapine (C)

ข้อเสนอแนะ: แพทย์ควรคำนึงว่าแนวทางการรักษาผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษานี้เป็นเพียงเครื่องมือที่จะช่วยให้แพทย์ปฏิบัติงานได้ง่ายขึ้นแต่ไม่สามารถทดแทนการตัดสินใจทางคลินิกของแพทย์ได้ การรักษาที่เหมาะสมสำหรับผู้ป่วยที่ไม่ตอบสนองต่อการรักษาควรเป็นการผสมผสานระหว่างการรักษาด้วยยาและการรักษาทางจิตสังคม การทำให้ชักด้วยไฟฟ้า (electroconvulsive therapy) ก็อาจเป็นทางเลือกหนึ่งในการรักษาผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองอย่างดีที่สุดยารักษาโรคจิตชนิดดั้งเดิม ในปัจจุบัน นิยามหรือเกณฑ์การระบุว่าผู้ป่วยเป็นโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาเป็นสิ่งที่ยังไม่สามารถหาข้อสรุปได้ ในการใช้แนวทางการรักษา นี้ แพทย์ควรคำนึงถึงข้อจำกัดในด้านต่างๆ ของแนวทางการรักษา ด้วย เช่น การค้นหาคำตอบ, เชื่อชาติของผู้ป่วยในงานวิจัย และสถานที่ทำการศึกษาวิจัย แนวทางการรักษา นี้จะมีผลต่อเวชปฏิบัติหรือไม่ยังเป็นสิ่งที่ต้องรอดูต่อไป

Guideline for the Pharmacotherapy of Treatment-Resistant Schizophrenia

**Disayavanish C, Srisurapanont M,
and the PTRS Guideline Working Group**

- This project was an academic activity of the Royal College of Psychiatrists of Thailand and supported by a grant from the Health Systems Research Institute (HSRI).
- The views and recommendations in this guideline are those of the working group and do not reflect the position of those two organizations.
- Printed on June 23, 1999 at the Department of Psychiatry, Faculty of Medicine, Chiang Mai University, Chiang Mai

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Abstract

Objectives: Treatment-resistant schizophrenia is a common problem in patients with schizophrenia that creates a huge economic burden for society. Since there has not been a guideline for the treatment of TRS, the PTRS Guideline Working Group, therefore, proposed to develop an evidence-based clinical practice guideline for the drug treatment of TRS.

Method: The PTRS Guideline Working Group comprised eleven psychiatrists, a psychologist, and a pharmacologist. A MEDLINE search was performed to identify the relevant articles published between 1966–1998. The evidence presented in 163 articles was extracted and graded by the use of a system modified from that of the Agency for Health Care Policy and Research (AHCPR). The strength of recommendations was categorized into A, B, and C.

Results: For a schizophrenic patient who does not respond to a classical antipsychotic, physicians should switch from the first classical antipsychotic to the second one, which belongs to a different class (A). A schizophrenic patient who does not respond to at least two adequate trials of classical antipsychotics should be classified as a TRS patient. For a TRS patient who is taking classical antipsychotic in high doses (at least 50 mg/day of haloperidol or its equivalence), a dose reduction strategy may be applied at this stage (B). In a TRS patient who is taking a usual dose of classical antipsychotic, clozapine should be considered as a first-line treatment (A). If a TRS patient does not respond to clozapine, physicians should add a classical antipsychotic to the ongoing clozapine, especially sulpiride (A) and loxapine (B). Risperidone should be considered in a TRS patient who refuses to have regular blood monitoring or have a contraindication for clozapine (A). Although there is no evidence supporting the use of olanzapine (or other atypical antipsychotics that will be available in the future) in a schizophrenic patient who resists both classical antipsychotics and risperidone, giving olanzapine (or other atypical antipsychotics that will be available in the future) may be worth a trial if the TRS patient refuses to take clozapine (C).

Discussion: Physicians should regard the PTRS Guideline as a tool for assisting their practice but not for replacing their clinical judgments. Optimal management for a TRS patient requires the integration of medical treatment with psychosocial interventions. Electroconvulsive therapy may be a treatment option for schizophrenic patients who fail to show adequate improvement with classical antipsychotics. The definition of or the set of criteria for TRS still cannot reach a conclusion. In using this guideline, physicians should be aware of its limitations, e.g., the search, the patients' ethnicity, the study cites. Whether this guideline will affect treatment practice remains to be seen.

Preface

This document describes the methods, process and recommendations of a guideline called “Guideline for the Pharmacotherapy of Treatment-Resistant Schizophrenia”. It describes explicitly the evidence used to support each recommendation made and is intended to form the source document from which summaries can be drawn. This guideline contains two parts which are: Part I. Introduction, Methods, Recommendations, and Discussion and Part II. The Review of Scientific Evidence.

The guideline was developed over a period of 16 months between December 1997 to May 1999. It includes scientific evidence relevant to the drug treatment of adult patients with treatment-resistant schizophrenia. The articles presented between 1966 to December 1998 were systematically reviewed and used for making recommendations. The guideline development was carried out as an academic activity of the Royal College of Psychiatrists of Thailand and supported by a grant from the Health Systems Research Institute (HSRI).

Due to the dearth of evidence relevant to psychosocial interventions for treatment-resistant schizophrenia and their variety, it has been difficult to make evidence-based recommendations. Therefore, we exclude them from the guideline. However, this does not mean that psychosocial interventions are not helpful for patients with treatment-resistant schizophrenia. The limited evidence has supported the administration of psychosocial interventions in these patients. **Therefore, optimal management for a TRS patient requires the integration of medical treatment with psychosocial interventions.**

Medical professionals should regard this guideline as a useful reference tool. This guideline is not intended to serve as a standard of medical care or replace clinical judgment. The recommendations also do not represent the only correct approach to every clinical situation. Physicians should keep in mind that patients may differ in their treatment preferences and capacities, history of response to previous treatments, family history of treatment response, and tolerance for different side effects. Standards of medical care should be determined on the basis of all clinical data available for an individual case and are subject to change, as scientific knowledge and technology advances and patterns evolve.

Like other scientific evidence, this guideline should be viewed as a part of clinical decision making. In everyday clinical practice, physicians should take their and their patients’ circumstances, as well as patients’ wishes, into account in making any clinical judgment.

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PART I

Development, Recommendations, and Discussion

Introduction

Selection of Topic

Schizophrenia is a serious psychiatric disorder. A review of epidemiological findings in several countries suggests that the morbid risk for schizophrenia is 0.5–1.6% (Jablensky 1995). The ethnic and geographic differences do not have much effect on the morbid risk.

Since schizophrenia usually occurs in the adolescent or early adulthood period, as well as its chronic course of illness, many young patients with schizophrenia lose their functions permanently. In addition, these patients also need a lot of support from their families and medical professionals. Hence, becoming a chronic schizophrenic patient is a crucial loss to the family, community, nation, and himself/herself. In addition, this problem creates a huge economic burden for society.

The discovery of classical antipsychotics in the 1950's is a major progress of schizophrenia treatment. However, many schizophrenic patients do not or only partially respond to those classical antipsychotics. A review shows that 20–40% of schizophrenic patients can be classified as those with treatment-resistant schizophrenia (TRS) (Schulz & Buckley 1995). TRS is an important problem in the health care system for many reasons. First, TRS is a prevalent problem in every community. Second, most TRS patients need a lot of social support since they have lost their ability to live independently. Last, they are frequently hospitalized and require long-term hospitalization.

While classical antipsychotics are the first-line treatment for most Thai schizophrenic patients, the treatment of choice for patients with TRS has been an issue of debate. Before the launch of atypical antipsychotics, physicians applied various strategies relevant to the administration of classical antipsychotics for treating TRS patients. The consensus on choosing a drug for TRS remains unsettled after the availability of atypical antipsychotics, e.g., clozapine, risperidone. While one guideline suggests the use of risperidone as a first-line treatment for TRS (McEvoy et al 1996), another supports the use of clozapine for this problem (American Psychiatric Association 1997). The major drawback of those two guidelines is that the suggestions are not developed under the extensive search of evidence relevant to TRS. This group, therefore, proposed to develop an evidence-based practice guideline relevant to drug use for TRS, called “**Guideline for the Pharmacotherapy of Treatment-Resistant Schizophrenia or PTRS Guideline**”.

Selection of Working Group Members and Editors of the Guideline

The working group comprised eleven psychiatrists, a psychologist, and a pharmacologist who were working in various institutions across the country. The grantees started preparing the first draft of the PTRS guideline and were considered as the guideline

editors. All working group members participated in editing the first draft, developing the second draft, and preparing the final version of the PTRS guideline.

The working group membership was (in alphabetical order):

- Chamlong Disayavanish, MD (Working Group Head and Editor)
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Clarification of Purposes

The PTRS Guideline was developed for the following purposes:

1. Develop an evidence-based clinical practice guideline for the drug treatment of TRS,
2. Diminish the differences of drug-use patterns in TRS patients, and

3. Diminish the unnecessary cost of inappropriate drug use in TRS patients.

Methods

The Review Process

A MEDLINE search (between 1966 and December 1998) was performed to find the studies relevant to the drug treatment for TRS. The search strategies were as follows: SCHIZOPHRENIA-DRUG-THERAPY and [REFRACTOR* or RESISTAN* or NONRESPON* or NON-RESPON* or UNRESPON*]. The review articles and the studies carried out in children and/or adolescents were excluded. The search was limited to the articles published in English.

Four hundred seventy-four articles were found by the MEDLINE search. To include an article for review, the inclusion criteria were as follows:

1. At least 60% of the participants diagnosed as TRS – as defined by any criteria (including TRS patients caused by intolerance to high doses of classical antipsychotics),
2. At least one drug or combination of drugs given for a period of time, and
3. The outcomes of the intervention (s) in the second criterion presented in at least one of the following aspects: i) response; ii) death; iii) relapse-exacerbation; iv) readmission; v) mental health in general; vi) psychotic symptoms; vii) positive symptoms; viii) negative symptoms; ix) quality of life or general health; x) functioning; and xi) cost saving.

Since most TRS patients are those who do not or partially respond to classical antipsychotics, unless otherwise specified, TRS patients mentioned in this guideline are nonresponders to classical antipsychotics.

Due to three reasons, results regarding drug adverse effects were excluded from the review process. First, the adverse effects of drugs used in TRS patients are not much different from those that occur in general schizophrenic patients. Second, in our opinion, the review of adverse effects occurred only in TRS patients is a process that discards a lot of evidence found in general schizophrenic patients. Last, conducting a review of drug adverse effects in general schizophrenic patients seems to be outside the scope of this guideline. However, the issue of drug adverse effects was also taken into consideration when making a recommendation.

One hundred sixty-three articles met all three inclusion criteria (Appendix 1). Initially, we classified them as short-term (12 weeks or less), medium-term (over 12 weeks to 26 weeks), and long-term studies (over 26 weeks). In the studies where multiple assessments were analyzed in the same term (short, medium or long), only the results of the last assessment in that term were extracted. The articles with an unclear duration of treatment were considered as short-term treatment articles. A few articles that used the mixing data of nonresponders to classical antipsychotics, clozapine, or risperidone were included in the section of classical antipsychotic nonresponders.

In each term of treatment, the studies were categorized according to the interventions as follows: i) placebo; ii) classical antipsychotics; iii) atypical antipsychotics; iv) lithium; v) anticonvulsants; vi) benzodiazepines; vii) drug combinations or augmentation treatments; and viii) other agents alone.

To abstract the data, we designed a data extraction form to collect the above-mentioned information (see Appendix 2). During the extraction process, every effort was made to abstract the data on an intention-to-treat basis. For dichotomous data, the dropout patients were, therefore, considered as patients with the worst outcomes. The dichotomous outcomes of interest were i) global nonresponse rate; ii) psychotic nonresponse rate; iii) death; iv) relapse or exacerbation rate; and v) readmission rate. The continuous data of interest were i) mental health in general; ii) psychotic symptoms; iii) positive symptoms; iv) negative symptoms; v) quality of life or general health; vi) functioning; and vii) cost saving.

The Process of Guideline Preparation

The issues concerned in making a recommendation were as follows:

1. Giving priority to the most rigorous scientific evidence,
2. Considering both benefits and harms of an intervention, including the calculation of odd ratio (OR) with 95% confidence interval (95% CI), and number needed to treat (NNT),
3. If appropriate, making a comparison across the studies by using a method for synthesizing the evidence, such as, meta-analysis, and
4. Taking the cost of long-term treatment into consideration.

We classified the study designs by using the system proposed by the Agency for Health Care Policy and Research (AHCPR) (Hadorn et al 1996). They were categorized into: i) randomized controlled trials (RCTs); ii) cohort studies; iii) case-control studies; iv) case series and registries; v) case reports; and vi) expert opinion.

We graded the levels of evidence by the use of a system modified from that of the AHCPR (Hadorn et al 1996). The levels of evidence in this guideline were categorized as follows:

Level 1 (L1): Supportive evidence from randomized controlled trials that included 100 patients or more,

Level 2 (L2): Supportive evidence from randomized controlled trials that included fewer than 100 patients,

Level 3 (L3): Supportive evidence from cohort studies,

Level 4 (L4): Supportive evidence from a case-control study,

Level 5 (L5): Supportive evidence from case series or case reports,

Level 6 (L6): Conflicting evidence with the weight of evidence supporting the recommendation, and

Level 7 (L7): Supportive evidence from a reported case or expert opinion.

In comparison to the original evidence hierarchy, this guideline only excluded the issues of study quality from its own evidence hierarchy. This was done because no system for grading study quality has been widely accepted.

In concordance with the levels of evidence (from L1 to L7), the recommendations in this guideline were categorized into A (from L1 to L3), B (L4 to L6), and C (L7).

The editors prepared the first draft of the guideline and distributed it to all working group members. The working group convened twice to discuss the guideline concepts and details. After each meeting, the editors edited the contents of the guideline in accordance with the working group's opinions.

Recommendations

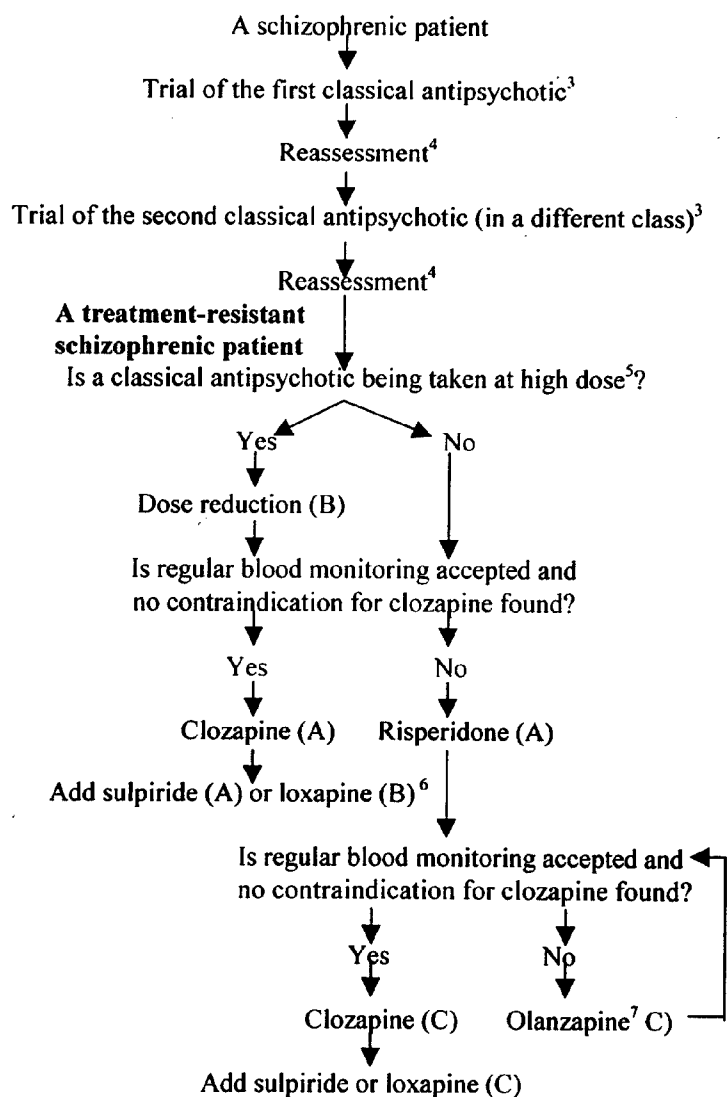
Since this guideline is relevant to the drug treatment of TRS only, physicians should use this guideline to accompany others that suggest the overview of treatment for schizophrenia, e.g., The Expert Consensus Guideline Series: Treatment of Schizophrenia (McEvoy et al, 1996), Practice Guideline for the Treatment of Patients with Schizophrenia (APA 1997), The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (Lehman et al, 1998), Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia (Canadian Psychiatric Association 1998).

A physician should review the clinical data, circumstances, and wishes of a classical antipsychotic nonresponder comprehensively before making a treatment plan. The correct diagnosis is crucial and should be reassessed. Some important issues that should be of concern are the history of response to previous treatment, the family history of treatment response, and the sensitivity and tolerance to drug adverse effects. All manageable causes that may impede the treatment response should be examined, for example, drug adverse effects, inadequate duration of treatment, unusual doses of antipsychotics, and drug interactions. Antipsychotic serum levels may be measured if possible. Since a schizophrenic patient usually loses his/her insight and ability to make a good judgment, the issue of compliance to medications should also be assessed. If appropriate, intramuscular long-acting antipsychotics may be given to a patient whose compliance to treatment is questioned.

Although the following recommendations are relevant to drug treatment, concomitant administration of psychosocial interventions should be provided for every TRS patient. In addition, if necessary, physicians may incorporate electroconvulsive therapy into their treatment plans. Flow chart 1 shows the recommended approach for a schizophrenic patient. Table 1 summarizes the results of trials drawn for making recommendations.

For a schizophrenic patient who does not respond to a classical antipsychotic, physicians should switch from the first classical antipsychotic to the second one, which belongs to a different class (A). Although the chance of that patient responding to this

Flow chart 1: Pharmacotherapy¹ of Treatment-Resistant Schizophrenia² (should be used to accompany the recommendations in the guideline)



¹ Administer psychosocial interventions or electroconvulsive therapy as appropriate.

² Choose the best treatment available according to the history of treatment response and clinical circumstances if the further step cannot be applied.

³ A 4- to 6- week trial of a classical antipsychotic equivalent to 400-600 mg/day of chlorpromazine.

⁴ Refer to the recommendations

⁵ At least 50 mg/day equivalent to haloperidol

⁶ Level C recommendation for other classical antipsychotics

⁷ Possibly include quetiapine and sertindole if they are available.

Table 1 Summary of the results of trials drawn for making recommendations

Source, year	Subjects and Study Design ^a	Measure indicating response ^b	Treatment, Total Subjects, Response Rate (RR) ^c	Significant Difference ^{b, d}
Kinon et al, 1993	Nonresponders to FPZ 20 mg/day, 8-week RCT	BPRS and CGI	FPZ 20mg/day, 17, RR = 1/17 FPZ 80 mg/day, 14, RR = 2/14 HAL 20 mg/day, 12, RR = 1/12	Chi-square for RR found NS
Collins et al, 1991	Nonresponders to APs, 4-week RCT		APs + lithium, 21, no RR APs, 22, no RR	Mann-Whitney U-test for MS and SANS scores found NS
Wilson, 1993	Nonresponders to CPZ, 8-week RCT	BPRS and SANS	HAL + lithium, 12, RR = 2/12 HAL + placebo, 10, RR = 2/10	N/A for RR, Mann-Whitney U-test for BPRS and SANS scores found NS
Simhandl et al, 1996	Nonresponders to APs, 6-week RCT		APs + carbamazepine, 15, no RR APs + lithium, 13, no RR APs + placebo, 14, no RR	Friedmann 2-way rank analysis for BPRS and CGI scores found NS
Van Putten et al, 1993	Nonresponders to HAL $\geq$ 50 mg/day, CS	CGI	Dose reduction, 13, RR = 6/13	
Kane et al, 1988	Nonresponders to HAL, 6-week RCT	BPRS and CGI	CZP, 126, RR = 38/126 (NRR = 88/126) CPZ, 136, RR = 5/136 (NRR = 136/141)	Fisher's exact test for RR found $p < 0.001$
Breier et al, 1994	Nonresponders to FPZ, 10-week RCT	BPRS	CZP, 18, RR = 8/18 (NRR = 10/18) HAL, 18, RR = 1/18 (NRR = 17/18)	Fisher's exact test for RR found $p = 0.017$
Hong et al, 1997	Nonresponders to APs, 12-week RCT	BPRS	CZP, 21, RR = 6/21 (NRR = 15/21) CPZ, 19, RR = 0/19 (NRR = 19/19)	N/A for RR
Rosenheck et al, 1997	Nonresponders to APs, 3-month RCT	PANSS	CZP, 122, RR = 44/122 (NRR = 78/122) HAL, 169, RR = 43/169 (NRR = 126/169) Pooled OR of NRR (95% CI) = 0.30 (0.20 to 0.45), NNT = 5	N/A for RR
Rosenheck et al, 1997	Nonresponders to APs, 6-month RCT	PANSS	CZP, 122, RR = 36/122 (NRR = 86/122) HAL, 169, RR = 18/169 (NRR = 151/169) OR of NRR (95% CI) = 0.29 (0.15 to 0.56), NNT = 5	N/A for RR
Rosenheck et al, 1997	Nonresponders to APs, 12-month RCT	PANSS	CZP, 122, RR = 51/122 (NRR = 71/122) HAL, 169, RR = 35/169 (134/169) OR of NRR (95% CI) = 0.37 (0.22 to 0.62), NNT = 5	N/A for RR
Shiloh et al, 1997	Nonresponders to CZP, 10-week RCT	BPRS	CZP + sulpiride, 16, RR = 8/16 (NRR = 8/16) CZP + placebo, 12, RR = 1/12 (NRR = 11/12) OR of NRR (95% CI) = 0.09 (0.01 to 0.88), NNT = 2	Chi-square for RR found $p < 0.02$
Mowernan & Siris, 1996	Nonresponders to CZP, CS	BPRS	CZP + loxapine, 7, RR = 7/7	
Still et al, 1996	Patients with nonresponse or intolerance to CZP, CS		RPD, 10, RR = 0/10	N/A for RR, Wilcoxon signed-rank test for PANSS scores found $p < 0.5$ (worsened)
Bondolfi et al, 1996 & 1998	Patients with nonresponse or intolerance to APs, 8-week RCT	PANSS	RPD, 43, RR = 29/43 CZP, 43, RR = 28/43	N/A for RR, ANCOVA for PANSS found NS
Conley et al, 1998	Nonresponders to APs, 8-week RCT	BPRS and CGI	OZP, 42, RR = 3/42 (NRR = 39/42) CPZ, 42, RR = 0/42 (NRR = 42/42) OR of NRR (95% CI) = 0.13 (0.01 to 2.65), NNT = 14	Fisher's exact test of RR found $p = 0.24$
Henderson et al, 1998	CZP responders, CS	BPRS	OZP, 19, RR = 8/19	

^a APs = Antipsychotics; CPZ = chlorpromazine; CZP = clozapine; FPZ = fluphenazine; HAL = haloperidol; RCT = randomized controlled trial; CS = case-series

^b BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms.

^c APs = Antipsychotics; CPZ = chlorpromazine; CZP = clozapine; FPZ = fluphenazine; HAL = haloperidol; OZP = olanzapine; RPD = risperidone; OR = odd ratio; NRR = nonresponse rate; NNT = number needed to treat.

^d N/A = not available; NS = not significant; RR = response rate.

strategy may be only about 9% (Kinson et al 1993), classical antipsychotic switching should be tried for two reasons. First, the next steps of treatment are expensive and may be complicated by blood monitoring. Second, this strategy is important to prove the treatment-resistant status of that patient.

A schizophrenic patient who does not respond to at least two adequate trials of classical antipsychotics should be classified as a TRS patient. Although the criteria set for TRS proposed by Kane et al (1988) has been widely used, the definition of an adequate drug trial tends to be less rigorous recently. According to the review of Conley and Buchanan (1997), a 4- to 6- week trial (rather than a strict 6 week one) of a classical antipsychotic equivalent to 400–600 mg/day (rather than at least 1000 mg/day) of chlorpromazine should be regarded as a standard for an adequate trial.^c

Although some experts suggest the augmentation of lithium or carbamazepine for classical antipsychotic nonresponders (Pantelis & Barnes 1996, Fleischhacker & Hummer 1997), a dearth of evidence can be found to support those suggestions. In addition, the results of most RCTs suggested that lithium (L2) (Collins et al 1991, Wilson 1993, Simhandl et al 1996) and carbamazepine (L2) (Simhandl et al 1996) have no or only a limited benefit for TRS patients. Due to these reasons, this guideline does not recommend the use of an augmentation strategy for the treatment of TRS. However, this strategy may be of benefit for controlling aggression and assaultive behavior (Johns and Thompson 1995). For the additional treatment of antiparkinson drugs or benzodiazepines, physicians may prescribe them as appropriate for the relief of extrapyramidal side effects, anxiety, and insomnia.

For a TRS patient who is taking classical antipsychotics in high doses (at least 50 mg/day of haloperidol or its equivalence), a dose reduction strategy may be applied at this stage (B) (Van Putten et al 1993). This strategy may improve a TRS patient's condition without increasing the treatment cost.

Although a variety of agents or strategies has shown some benefits in treating TRS, clozapine should be considered as a first-line treatment for two reasons (A). First, the benefit of clozapine has been supported by evidence at the level of L1 in short-term, medium-term, and long-term treatment (Kane et al 1988, Breier et al 1994, Hong et al 1997, Rosenheck et al 1997). Second, the benefits of other agents, including risperidone, have been rarely replicated. According to the short-term results of those four RCTs, the chance of a TRS patient improving by the use of this strategy is about 29–44%. In addition, clozapine is significantly more effective than classical antipsychotics at the pooled nonresponse-rate OR (95% CI) of 0.30 (0.20 to 0.45). The NNT of 5

also indicates that 1 of every 5 TRS patients whose classical antipsychotics are substituted by clozapine will be switched from a nonresponder to a responder. Since its effectiveness is well established, clozapine should also be reconsidered whenever a TRS patient fails to respond to the treatment strategies described below.

With respect to the treatment cost, clozapine appears to increase the cost of outpatient treatment but saves on that of inpatient treatment. However, its ability to save the total cost of treatment is still controversial (Rosenheck et al 1997).

Although drug-induced agranulocytosis is a major drawback of clozapine, with regular blood monitoring, it is a safe treatment for TRS patients. By using the standard system for monitoring the number of white cells, only 2.9%, 0.8%, and 0.03% of 6,316 registered patients developed neutropenia, agranulocytosis, and fatal agranulocytosis, respectively (Atkin et al 1996).

For a TRS patient who does not respond to clozapine, physicians should add a classical antipsychotic to the ongoing clozapine, especially sulpiride (A) (OR with 95% CI of 0.09 with 0.01–0.88, NNT = 2) (Shiloh et al 1997) and loxapine (B) (Mowerman et al 1996). Switching clozapine to risperidone is not recommended since it may worsen psychotic symptoms (B) (Still et al 1996).

Despite the fact that the administration of clozapine with regular blood monitoring is very safe, some TRS patients may refuse to have regular blood monitoring or have a contraindication for clozapine. As the results of an RCT indicate that risperidone is as effective as clozapine (Bondelfi et al 1996, Bondelfi et al 1998), risperidone should be considered in this kind of patient (A). The recommendation for the use of risperidone as a second-line treatment is supported by two reasons. First, available evidence relevant to the use of risperidone for TRS patients is only at the level of L2, which is not as strong as that for clozapine. Second, its benefit in medium- and long-term treatment has not been clear. Although an RCT comparing the efficacy and safety between risperidone and a classical antipsychotic is important to compute an OR (95% CI) and an NNT, no such trial can be found so far.

There have been very few studies of olanzapine in TRS patients. The paucity of evidence shows that, not different from chlorpromazine, olanzapine improves the TRS patients' psychopathology modestly (A) (Conley et al 1998). Olanzapine is not significantly more effective than chlorpromazine at the nonresponse-rate OR (95% CI) of 0.13 (0.01–2.65) and the NNT of 14.

Olanzapine may be given to a TRS patient who responds but wishes to discontinue clozapine (B) (Henderson et al 1998). However, this strategy should be applied with caution since the condition of some patients may be worse. In addition, at least one to two weeks should be expected for tapering clozapine (C) (Shore 1995).

Although there is no evidence supporting the use of olanzapine (or other atypical antipsychotics that will be available in the future) in a schizophrenic patient who resists

both classical antipsychotics and risperidone, giving olanzapine (or other atypical antipsychotics that will be available in the future) may be worth a trial if the TRS patient refuses to have regular blood monitoring or has a contraindication for clozapine (C).

Discussion

Physicians should regard the PTRS Guideline as a tool for assisting their practice but not for replacing their clinical judgments. Like other scientific evidence, the guideline should be viewed as a part of clinical decision making. Standards of medical care should be determined on the basis of all clinical data available for an individual case. In addition, the physicians' and patients' circumstances, as well as patients' wishes, should be taken into account when making any clinical judgment.

Due to the dearth of evidence relevant to psychosocial interventions and the variety of interventions for TRS, this issue has made evidence-based recommendations difficult. Therefore, we exclude them from the guideline. However, this does not mean that psychosocial interventions are not helpful for patients with TRS. The limited evidence has supported the administration of psychosocial interventions in these patients. Therefore, optimal management for a TRS patient requires the integration of medical treatment with psychosocial interventions.

Some limited evidence suggests that ECT could be beneficial for some of those who have shown a limited response to antipsychotic medication (Tharyan 1998). The short term beneficial effect of ECT may be of particular relevance in situations where speed of improvement is important. There is also a suggestion that ECT added to antipsychotic medication treatment may hasten discharges from hospital and reduce relapse rates in the medium to long term. This suggests a role for the addition of a trial of ECT as a treatment option in those with schizophrenia who fail to show adequate improvement with conventional antipsychotics. The administration of ECT is particularly relevant in developing countries, where atypical and newer antipsychotics like clozapine, risperidone, and olanzapine may not be practical alternatives due to nonavailability, high cost, and/or the inconvenience of hematological monitoring.

Although TRS is a prevalent problem in psychiatric practice, its definition or set of criteria cannot reach a conclusion. Applying a loose definition or set of criteria may cover a schizophrenic patient who is not really resistant to classical antipsychotics. A strict definition or set of criteria may be difficult to apply in everyday clinical practice. This issue should be considered as a clinical problem for patients, physicians, and investigators since it plays a role in causing the variation of treatments and treatment responses. While the accepted definition or set of criteria of TRS is still an issue of debate, some atypical antipsychotics (e.g., olanzapine, quetiapine, risperidone) have gained more acceptance for becoming a first-line treatment (Shon et al 1999). In addition, some experts tend to give an atypical antipsychotic to a schizophrenic patient who only resists to a classical antipsychotic (McEvoy et al 1996). In the future, TRS may have to be classified into many categories, e.g., nonresponders to two classical antipsychotics, nonresponders to two atypical antipsychotics, etc.

The issue of adequate doses of classical antipsychotics also remains unsettled. The daily doses, equivalent to 400–600 mg of chlorpromazine, proposed in this guideline appear to be much lower than those suggested by Kane et al (1988). However, the daily doses suggested in this guideline are in concordance with two comprehensive reviews (Baldessarini et al 1988, Dixon et al 1995). According to those reviews, the upper end of the optimal daily doses of classical antipsychotics may be at 700–750 mg equivalent to chlorpromazine. While daily doses higher than this may yield lesser degrees of improvement, dose reduction has proved to be one effective strategy in treating TRS.

The PTRS Guideline recommendation for the use of clozapine as a first-line treatment for TRS appears to be in concordance with those of other practice guidelines (McEvoy et al 1997, American Psychiatric Association 1997, Lehman 1998, Canadian Psychiatric Association 1998). In comparison to those guidelines, the disadvantage of this guideline appears to be its limited scope that covers only the issue of drug treatment for TRS. However, due to its narrower scope, the comprehensive search of scientific evidence relevant to the drug treatment of TRS was made possible. It can be seen that, about the drug treatment of TRS, the recommendations of this guideline are more elaborated and more practical than those of other guidelines.

This guideline should be viewed with some limitations. First, some relevant articles may be beyond the coverage of the MEDLINE search. The results of a study showed that at least 18% of the RCTs published in medical journals may not be found by the MEDLINE search (Dickersin et al 1994). Second, most data included in this guideline are obtained from the studies carried out in western patients and settings. Although this issue was considered during the development of the PTRS Guideline, physicians should be aware of this limitation and may have to make their own judgments in treating an individual patient with TRS. Last, apart from clozapine, other atypical antipsychotics are only at the beginning stage of clinical trials in TRS patients. It can be expected that, within a few years, the evidence in this issue will increase enormously and lead to the revision of the PTRS Guideline.

Implementation of the PTRS Guideline is also another purpose of this development. Although this guideline was developed to be a practical and user-friendly one, whether it will affect treatment practice remains to be seen. Physicians' decisions to apply or not to apply the PTRS Guideline in their clinical practice should be assessed further. The understanding of physicians' behavior in this issue will be helpful in revising the PTRS Guideline and the development of other clinical practice guidelines.

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PART II

The Review of Scientific Evidence ^{1,2}

Short-Term Treatment for Classical Antipsychotic Nonresponders: Atypical Antipsychotics

Fifty articles studying the benefits of atypical antipsychotics alone or comparing the benefits between atypical antipsychotic and classical antipsychotics were included in this section.

Clozapine

The results of four RCTs suggested the superiority of clozapine with respect to improving mental health, as well as relieving psychotic, positive, and negative symptoms (L1) (Kane et al 1988a, Breier et al 1994, Hong et al 1997, Rosenheck et al 1997). Since the studies of Conley et al (1988), Herrera et al (1988), Kane et al (1988b), Breier et al (1993), Rosenheck et al (1998a), Rosenheck et al (1998b), and Rosenheck et al (1998c) are parts of three trials presented by Kane et al (1988a), Breier et al (1994), and Rosenheck et al (1997), the results of these seven studies were not taken into account.

Due to the strong evidence obtained from those RCTs, the results of several non-RCTs were not considered (Small et al 1987, Mattes 1989, Meltzer et al 1989a, Naber et al 1989, Meltzer et al 1990, Davidson et al 1993, Hagger et al 1993, Kahn et al 1993, Kuoppasalmi et al 1993, Zito et al 1993, Lieberman et al 1994, Miller et al 1994a, Miller et al 1994b, Stern et al 1994, Welch et al 1994, Arranz et al 1995, Jin et al 1995, Kronig et al 1995, Kurz et al 1995, Hoff et al 1996, Nagamoto et al 1996, Litman et al 1996, Brown et al 1997, Chong et al 1997, Wong et al 1997).

Although the results of two RCTs showed that the low blood levels of clozapine (50–150 ng/ml) were less effective than the higher ones (Potkin et al 1994; Vander Zwaag et al 1996), the appropriate blood levels of clozapine are not yet known (L6). While one study suggested the appropriate blood levels of at least 200 ng/ml (Vander Zwaag et al 1996), the other suggested those of at least 420.5 ng/ml (Potkin et al 1994). The results of three non-RCTs suggested that clozapine blood levels should be at least 300–350 ng/ml (Perry et al 1991, Liu et al 1996, Chong et al 1997).

Al Semaan (1996) reported a patient with TRS who responded to the combination of clozapine and bromocriptine (L5).

Risperidone

Risperidone was compared to clozapine in an RCT (L2) (Bondelfi et al 1998, Bondelfi et al 1996). The response rates and severity of psychotic symptoms of both treated groups were not significantly different. The results of two non-RCTs supported the

¹ The sequence of review content was arranged upon the strength of evidence.

² The strategy to grade the level of evidence from L1 to L7 can be seen in the section of “The Process of Guideline Preparation” in Part I.

use of risperidone alone (L5) (Warner et al 1996) and the combination of risperidone and classical antipsychotics (L5) (Bacher & Kaup 1996).

Olanzapine

While the results of an RCT showed that olanzapine was not more effective than chlorpromazine in treating TRS patients (L2) (Conley et al 1998a), a cohort study found the benefits of olanzapine on mental health in general and psychotic symptoms (L5) (Martin et al 1997).

However, olanzapine might be of benefit in improving social function (L5) (Sheitman et al 1997), and for TRS patients who have a greater tendency for classical antipsychotic side effects and tardive dyskinesia (L5) (Conley et al 1998b).

Short-Term Treatment for Classical Antipsychotic Nonresponders: Classical Antipsychotics

All studies comparing atypical antipsychotics and classical antipsychotics were included in the above part — short-term treatment for classical antipsychotic nonresponders: atypical antipsychotics. Forty-seven articles relevant to the administration of classical antipsychotics, including dose adjustment, classical antipsychotic switching, and adjunctive treatments, were included in this section.

Dose Reduction

A case-series study of Van Putten et al (1993) reported the benefit of a dose-reduction strategy in relieving psychotic symptoms (L5). Because the report of Liberman et al (1994) was the republication of the one of Van Putten et al (1993), the later report was not taken into account in this review. Moreover, Darby et al (1995) reported that almost half of the TRS patients could be discharged by using this strategy (L5). However, the effectiveness in improving the patients' mental health in general, as measured by Clinical Global Impression (CGI), was not clear.

High-Dose Regimen

The benefits of a high-dose regimen have not been shown explicitly (L6). While two RCTs reported some benefits from this strategy (McCreadie & Macdonald 1977, Dencker et al 1978), the other four RCTs found none (McCreadie et al 1979, Hollister et al 1987, Huang et al 1987, Kinon et al 1993). Moreover, an RCT carried out by Quitkin et al (1975) showed the inferiority of a high-dose regimen.

Due to several lines of evidence from those RCTs, the results of some non-RCTs were not considered in this review (Rifkin et al 1971, Lehmann et al 1981, Riman et al 1981, Van Putten et al 1981, Kim & Hollister 1984).

Classical Antipsychotic Switching

An appropriate study design to find out the benefits of classical antipsychotic switching is the use of a randomized controlled trial comparing the efficacy of substituted classical antipsychotics with that of the ongoing one. The results of an RCT using this study design indicated the limited benefit of this strategy (L2) (Kinon et al 1993).

An effective classical antipsychotic that should be given to a TRS patient has also been an issue of debate (L6). After TRS patients did not respond to classical antipsychotics, some investigators switched from the first classical antipsychotics to other ones. In an RCT switching the first noneffective antipsychotics to two classical antipsychotics, mesoridazine produced a significantly greater improvement than thioridazine (Gardos 1978). In contrast, two RCTs found no difference of efficacy among haloperidol, thioridazine, and fluphenazine (Hall et al 1968, Gonier et al 1970).

Due to the several lines of evidence from RCTs, the results of some non-RCTs were not considered in this review (Wolpert et al 1967, Deniker et al 1980, Dencker et al 1981, Vital-Herne et al 1986, Feinberg et al 1988, Shalev et al 1993).

Augmentation Treatment

Several studies investigated the addition of some agents to ongoing classical antipsychotics in order to improve TRS patients' condition. The results of many RCTs showed the benefits of adding some agents to ongoing classical antipsychotics. Those were glycine (L2) (Heresco Levy et al 1996) and fenfluramine (L2) (Marshall et al 1989). However, the benefits of adding glycine should be viewed with caution since the results of a non-RCT showed only small benefits from this practice (L5) (Costa et al 1990). No or only a limited benefit was found in the augmentation of ceruletide (L2) (Hommer et al 1984), lithium (L2) (Collins et al 1991, Wilson 1993, Simhandl et al 1996), and carbamazepine (L2) (Simhandl et al 1996).

Some augmentation agents that showed their benefits in non-RCTs were physostigmine (cholinesterase inhibitor) (Rosenthal & Bigelow 1973), doxepine (Ketani 1976), chloroquine (Traficante et al 1977), reserpine (Bacher & Lewis 1981, Bacher & Lewis 1985), diazepam (Nestoros et al 1983), phenobarbital (Prakash et al 1984), fenfluramine (Kolakowska et al 1987), proglumide (cholecystokinin antagonist) (Hicks et al 1989), fluoxetine (Goff et al 1990), bromocriptine (Wolf et al 1992), famotidine (Oyewumi et al 1994, Rosse 1996), and idazoxan (alpha 2 antagonist) (Litman et al 1996). However, the addition of dihomogammalinolenic acid (DHGLA) contributed no benefit for treating TRS patients (L2) (Vaddadi et al 1986).

Some experts suggested the use of combined electroconvulsive therapy and classical antipsychotics for TRS patients (L7) (McNeill 1977, Fink 1987).

Short-Term Treatment for Classical Antipsychotic Nonresponders: Other Agents Alone

Thirteen articles relevant to the use of other agents alone were included in this section.

Anticonvulsants

No benefit from giving carbamazepine to TRS patients was found in a cohort study (L5) (Sramek et al 1988).

Lithium

The results of a case-series study supported the use of lithium alone (L5) (Shalev et al 1987).

Other agents

The benefits of cholecystokinin were found in a cohort study (L5) (Boza & Rotondo 1985), but not in the other two RCTs (L2) (Hommer et al 1985, Peselow et al 1987). Some benefits were found in giving some agents, including combined L-dopa and carbidopa (L7) (Kay & Opler 1985–1986), bromocriptine (L5) (Wells et al 1991), etizolam (L7) (Benazzi et al 1993), and glycine (L2) (Javitt et al 1994).

Some agents have been proven to have no benefits in treating TRS patients. Those are propranolol (L5) (Elizur et al 1979), dihomogammalinolenic acid – a prostaglandin E1 precursor (L2) (Vaddadi et al 1986), and nifedipine (L5) (Kramer et al 1987).

Medium-Term Treatment for Classical Antipsychotic Nonresponders

Thirty articles reporting the results of medium-term treatment were included in this section.

Clozapine

In medium-term treatment, the efficacy of clozapine was shown in an RCT (L1) (Rosenheck et al 1997, Rosenheck et al 1998a, Rosenheck et al 1998b, Rosenheck et al 1998c). Owing to those results, the evidence from non-RCTs was not considered in the review (Meltzer et al 1989, Meltzer et al 1990, Pickar et al 1992, Clozapine Study Group 1993, Hasegawa et al 1993, Hagger et al 1993, Kuoppasalmi et al 1993, Drew et al 1994, Lieberman et al 1994, Lindermayer et al 1994, Lindstrom 1994, Miller et al 1994, Chow et al 1995, Honer et al 1995, Meltzer & Okayli 1995, Abraham et al 1997, Spivak et al 1997b, Connelly et al 1998).

Although the results of a cohort study supported the administration of clozapine at the blood levels of at least 370 ng/ml (L5) (Hasegawa 1993), those of another study did not show any beneficial differences between high-dose (mean 525 mg/day) and low-dose clozapine (294 mg/day) (L5) (Gordon & Milke 1996).

Risperidone

The medium-term effects of risperidone are still controversial (L6). While a study found that risperidone was not as effective as clozapine (L3) (Flynn et al 1998), another found the comparable therapeutic effects of both drugs (L3) (Lindermayer et al 1998).

Olanzapine

A case-series study found the benefit of olanzapine on psychotic symptoms (L5) (Martin et al 1997).

Other agents

Two cohort studies found the benefits of high-dose haloperidol (L5) (Psaras et al 1980) and the addition of reserpine to an ongoing classical antipsychotic (L5) (Bacher & Lewis 1978).

Three non-controlled studies found the benefits of: i) a combination of penicillin and primrose oil (which can increase prostaglandin) in 2 TRS patients (L5) (Vaddadi 1979); ii) verapamil (L7) (Bloom et al 1987); and iii) the addition of valproate to an ongoing classical antipsychotic (L5) (Moringo et al 1989).

Long-Term Treatment for Classical Antipsychotic Nonresponders

Thirty-two articles relevant to the long-term treatment of classical antipsychotic responders were included in this section.

Efficacy

The results of an RCT showed that clozapine was helpful for a wide range of psychotic symptoms but not for quality of life and cost saving (L1) (Rosenheck et al 1997, Rosenheck et al 1998a, Rosenheck et al 1998b, Rosenheck et al 1998c). The long-term benefits of clozapine were also shown in several non-RCTs (Lindstrom 1989, Mattes 1989, Meltzer et al 1989a, Meltzer et al 1989b, Revicki et al 1990, Breier et al 1993, Kuoppasalmi et al 1993, Zito et al 1993, Lindstrom 1994, Manschreck et al 1994, Miller et al 1994, Jonsson & Walinder 1995, Tanner et al 1995, Wilson 1996, Conley et al 1997, Herman 1997, Sajatovic et al 1998, Spivak et al 1998).

Risperidone could not improve clinical function and aggressive behavior (L3) (Beck et al 1997).

The benefits of some antipsychotics were shown in a few studies, including zotepine – an atypical antipsychotic (L5) (Harada et al 1987), levomepromazine (L5) (Lal & Nair 1992), and butaperazine (L5) (Itil et al 1966).

A study reported the benefits of adding valproate to ongoing classical antipsychotics (L5) (Moringo et al 1989).

Rosse et al (1995) reported a TRS patients who responded to the addition of famotidine to ongoing molindone (L7).

Economic Issues

Only the long-term studies examined the cost of treatment for TRS. Although five non-RCT studies showed that clozapine could save on the total cost of treatment for TRS patients by saving on hospitalization (Revicki et al 1990, Davies & Drummond 1993, Meltzer et al 1993, Manschreck et al 1994, Jonsson & Walinder 1995), an RCT could not do so (L1) (Rosenheck et al 1997, Rosenheck et al 1998a, Rosenheck et al 1998b, Rosenheck et al 1998c). However, all six studies found that clozapine could save the cost of inpatient treatment but increase the drug and outpatient-treatment

costs. Probably due to this reason, an initiation of clozapine treatment in TRS outpatients could not save on the cost of treatment (L5) (Luchins 1998).

Short-Term Treatment for Classical Antipsychotic Nonresponders with Special Characteristics

Sixteen articles relevant to the short-term treatment of classical antipsychotic nonresponders with special characteristics were included in this part.

The results of an RCT showed that sulpiride adjunction to clozapine significantly improved the general, positive, and negative schizophrenic symptoms of nonresponders to classical antipsychotics and clozapine (L2) (Shiloh et al 1997). Three treatment strategies for nonresponders to both classical antipsychotics and clozapine were investigated in three cohort studies. The addition of a classical antipsychotic (loxapine) to clozapine was a promising approach (L5) (Mowerman et al 1996). The benefits of adding a selective serotonin reuptake inhibitor (fluvoxamine) to clozapine were not clear (L5) (Silver et al 1996). Switching from clozapine to risperidone worsened psychotic and positive symptoms (L5) (Still et al 1996).

Olanzapine could maintain the patients' condition in 8 of 19 TRS patients who had been stabilized by clozapine but wished to have an olanzapine trial (L5) (Henderson et al 1998).

A case report presented that the combination of olanzapine and lithium might be beneficial for the nonresponders to both classical antipsychotics and risperidone and those intolerable to clozapine (L7) (Thomas and Labbate 1998).

The benefits of using clozapine for TRS patients with special characteristics were shown in some case-series studies (L5), including patients with brain dysmorphology (Lauriello et al 1998), extrapyramidal side effects (Spivak et al 1997a), the first episode of schizophrenia (Szymanski et al 1994), prominent negative symptoms (Lindermayer et al 1994), and mental retardation (Sajatovic et al 1994).

Adding fluvoxamine to clozapine was useful for TRS patients who had developed obsessive-compulsive symptoms after taking clozapine (L5) (Poyurovsky et al 1996). The results of a case-series study showed the benefits of using clozapine in classical antipsychotic nonresponders with polydipsia. In that study, clozapine not only relieved the psychotic symptoms but also decreased the severity of polydipsia (L5) (Fuller et al 1996).

A case-series study reported that the addition of cyproheptadine to classical antipsychotics was helpful for nonresponders to classical antipsychotics and the combination of fluoxetine and classical antipsychotics (L5) (Bacher et al 1994).

Giving clozapine to a TRS patient with a history of classical antipsychotic-induced agranulocytosis showed that clozapine was helpful in relieving psychotic symptoms and did not induce agranulocytosis (L7) (Bauner & Mackert 1994).

At the time of review, there was insufficient information to answer several important questions about the magnitude or specificity of clinical problems associated with clozapine discontinuation. However, at least one to two weeks should be expected for tapering clozapine (L7) (Shore 1995).

Appendices

Appendix 1: Studies Included in the Review

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Appendix 2

Data Extraction Form for PTRS Guideline

Article No.....

Article Identification: Author (s)Year of Publication

From A and B, this article was ☐ included ☐ excluded

Cost-of-treatment article ☐ yes ☐ no

A. Inclusion criteria for an article

☐ 1. At least 60% of the participants diagnosed as TRS - as defined by any criteria (including TRS caused by intolerance to the high doses of classical antipsychotics)

☐ 2. At least one drug or combination of drugs given for a period of time

☐ 3. The outcomes of the intervention (s) in the second criteria presented in at least one of the following aspects: i) response; ii) death; iii) relapse/exacerbation; iv) readmission; v) mental health in general; vi) psychotic symptoms; vii) positive symptoms; viii) negative symptoms; ix) QOL or general health; x) functioning; and xi) cost saving

B. Any reason for the exclusion of the article (specified)

C. Article classification

1. Duration of the study (If the duration of a study varies from case to case, choose the mean duration first, otherwise choose the shortest one)

1.1 Short-term (≤ 12 wks or ≤ 3 mos) ☐ yes ☐ no

1.2 Medium-term (13-26 wks or 13 wks to 6 mos) ☐ yes ☐ no

1.3 Long-term (> 27 weeks or > 6 mos) ☐ yes ☐ no

2. Studied subjects

☐ 2.1 Classical-antipsychotic resistant

☐ 2.2 Other drug resistant (specified)

☐ 2.3 Subjects with special characteristics (specified)

3. Studied drugs

☐ 3.1 Placebo

☐ 3.2 Classical antipsychotic (specified)

☐ 3.3 Atypical antipsychotic (specified)

☐ 3.4 Lithium

☐ 3.5 Anticonvulsant (specified)

☐ 3.6 Benzodiazepines (specified)

☐ 3.7 Drug combination 1 (specified)

☐ 3.8 Drug combination 2 (specified)

☐ 3.9 Adjunct drug 1 (specified)

☐ 3.10 Adjunct drug 2 (specified)

☐ 3.11 Others (specified)

4. Methodology

☐ 4.1 Randomized-controlled trial

☐ 4.2 Cohort study (prospective study in well defined TRS patients)

☐ 4.3 Case-control study (retrospective study in patients without TRS)

☐ 4.4 Case series and registries (data from patients' records)

☐ 4.5 Case report and expert opinion (data from a patient's record)

☐ 4.6 Others (specified)

In extracting the data regarding responders/nonresponders, use the definition defined by the investigators first. If the definition is not available, the reviewers will rate a patient with a CGI score of at least much improved as a global responder. In the same way, the reviewers will rate a patient with a decreased BRPS score of at least 20% as a psychotic responder.

I. Term: [] Short-term [] Medium-term [] Long-term

A. Dichotomous Data (intention-to-treat; dropouts = pts w worst outcome)

Drug/Drug-combo 1:; No. of pts at entry; No. of dropouts

No of pts: w/o global response; w/o psychotic response.....

No of pts: w death; w relapse/exacerbation; w readmission

Drug/Drug-combo 2:; No. of pts at entry; No. of dropouts

No of pts: w/o global response; w/o psychotic response.....

No of pts: w death; w relapse/exacerbation; w readmission

Drug/Drug-combo 3:; No. of pts at entry; No. of dropouts

No of pts: w/o global response; w/o psychotic response.....

No of pts: w death; w relapse/exacerbation; w readmission

B. Measures and significant benefits (>)/nonsignificant differences (=) (consider both dichotomous or continuous data; if contrast, priority is given to continuous data)

1. Mental health - general: > / = > / =

2. Psychotic symptoms: > / = > / =

3. Positive symptoms: > / = > / =

4. Negative symptoms: > / = > / =

5. QOL or general health: > / = > / =

6. Functioning: > / = > / =

7. Cost saving: > / = > / =

II. Term: [] Short-term [] Medium-term [] Long-term

A. Dichotomous Data (intention-to-treat; dropouts = pts w worst outcome)

Drug/Drug-combo 1:; No. of pts at entry; No. of dropouts

No of pts: w/o global response; w/o psychotic response.....

No of pts: w death; w relapse/exacerbation; w readmission

Drug/Drug-combo 2:; No. of pts at entry; No. of dropouts

No of pts: w/o global response; w/o psychotic response.....

No of pts: w death; w relapse/exacerbation; w readmission

Drug/Drug-combo 3:; No. of pts at entry; No. of dropouts

No of pts: w/o global response; w/o psychotic response.....

No of pts: w death; w relapse/exacerbation; w readmission

B. Measures and significant benefits (>)/nonsignificant differences (=) (consider both dichotomous or continuous data; if contrast, priority is given to continuous data)

1. Mental health - general: > / = > / =

2. Psychotic symptoms: > / = > / =

3. Positive symptoms: > / = > / =

4. Negative symptoms: > / = > / =

5. QOL or general health: > / = > / =

6. Functioning: > / = > / =

7. Cost saving: > / = > / =

Note:

