Guideline for the Pharmacotherapy of Treatment-Resistant Schizophrenia†

CHAMLONG DISAYAVANISH, M.D.*,
PICHET UDOMRATN, M.D.**,
DUANGJAI KASANTIKUL, M.D.***;
THIENCHAI NGAMTIPWATTHANA, M.D.*****,
POONSRI RANGSEEKAJEE, M.D.*******,
PRAMOTE SUKANICH, M.D.*********,
TAWEESIN VISANUYOTHIN, M.D.**********
MANIT SRISURAPANONT, M.D.*,
PRIMPRAO DISAYAVANISH, Ph.D.*,
PONGSATORN NETRAKOM, M.D.****,
SRICHAN PHORNCHIRASILP, Ph.D.******,
PAITOON SAMUTHRSINDH, M.D.********,
KITTIWAN THIAM-KAEW, M.D.**********,

Abstract

The authors proposed to develop an evidence-based guideline relevant to drug use for treatment-resistant schizophrenia (TRS), which will be called "Guideline for the Pharmacotherapy of Treatment-Resistant Schizophrenia or PTRS Guideline". The authors performed a MEDLINE search (between 1966 and December 1998) and classified the study designs of those trials by using the system proposed by the Agency for Health Care Policy and Research (AHCPR). The levels of evidence were graded and recommendations were made by the use of a system modified from that of the AHCPR. One hundred and sixty-three articles met the inclusion criteria for the review. For a schizophrenic patient who does not respond to a classical antipsychotic,

* Department of Psychiatry, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200,
** Department of Psychiatry, Faculty of Medicine, Prince of Songkla University, Songkhla 90112,
*** Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330,
**** Department of Psychiatry and Neurology, Phramongkutklao Hospital and College of Medicine, Bangkok 10400,
***** Department of Psychiatry, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700,
****** Department of Pharmacology, Faculty of Pharmacy, Mahidol University, Bangkok 10400,
******* Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002
******** Srithanya Hospital, Nonthaburi 11000,
********* Department of Psychiatry, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400,
********** Suanprung Psychiatric Hospital, Chiang Mai 50200,
*********** Somdet Chaopraya Hospital, Bangkok 10600, Thailand.

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† The views and recommendations in this guideline are those of the working group and do not reflect the position of those two organizations.
† The full report of this guideline can be viewed at http://go.to/ptrsguideline

physicians should switch from the first classical antipsychotic to the second one, which belongs to a different class. A schizophrenic patient who does not respond to at least two adequate trials of classical antipsychotics should be classified as a TRS patient. Clozapine should be considered as a first-line treatment for TRS. Risperidone should be considered in a TRS patient who refuses to have regular blood monitoring or has contraindication for clozapine. Physicians should use this guideline to accompany others that suggest the overview of treatment for schizophrenia. Appropriate application and the limitations of the guideline are also discussed.

Key word : Treatment Resistant Schizophrenia, Pharmacotherapy, Guideline

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Schizophrenia is a serious psychiatric disorder with a morbid risk of 0.5–1.6 per cent[1]. Since it 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. 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 was 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 per cent of schizophrenic patients can be classified as those with treatment-resistant schizophrenia (TRS)[2]. This clinical condition 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.

Before the launch of atypical antipsychotics, physicians applied various strategies relevant to the administration of classical antipsychotics for treating TRS patients. Although the issue of drug treatment for TRS has been concerned by some recent guidelines for the treatment of schizophrenia, only brief statements suggesting the use of clozapine are given without many details[3-6]. Some important issues are not mentioned in those guidelines, such as, alternatives to clozapine, the response (or nonresponse) rate, and number needed to treat (NNT). Due to this, it is difficult to apply those recommendations in everyday clinical practice. Therefore, the authors proposed to develop an evidence-based guideline relevant to drug use for TRS, which was called "Guideline for the Pharmacotherapy of Treatment-Resistant Schizophrenia or PTRS Guideline".

MATERIAL AND METHOD

The guideline was developed over a period of 16 months between December 1997 and May 1999. 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*]. Review articles and studies carried out in children and/or adolescents were excluded. The search was limited to articles published in English.

To include an article for review, the inclusion criteria were as follows:

1. At least 60 per cent 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.

Due to three reasons, results regarding adverse drug 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 occurring only in TRS patients is a process that discards a lot of evidence found in general schizophrenic patients. Last, conducting a review of adverse drug effects in general schizophrenic patients seems to be outside the scope of this guideline. However, the issue of adverse drug effects was also taken into consideration when making a recommendation.

Initially, we classified the included trials 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.

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. 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.

We classified the study designs of those trials by using the system proposed by the Agency for Health Care Policy and Research (AHCPR)[7]. 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 [7]. 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 excluded only 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.

RESULTS

The MEDLINE search found 474 articles. Of those, 163 articles met all three inclusion cri-

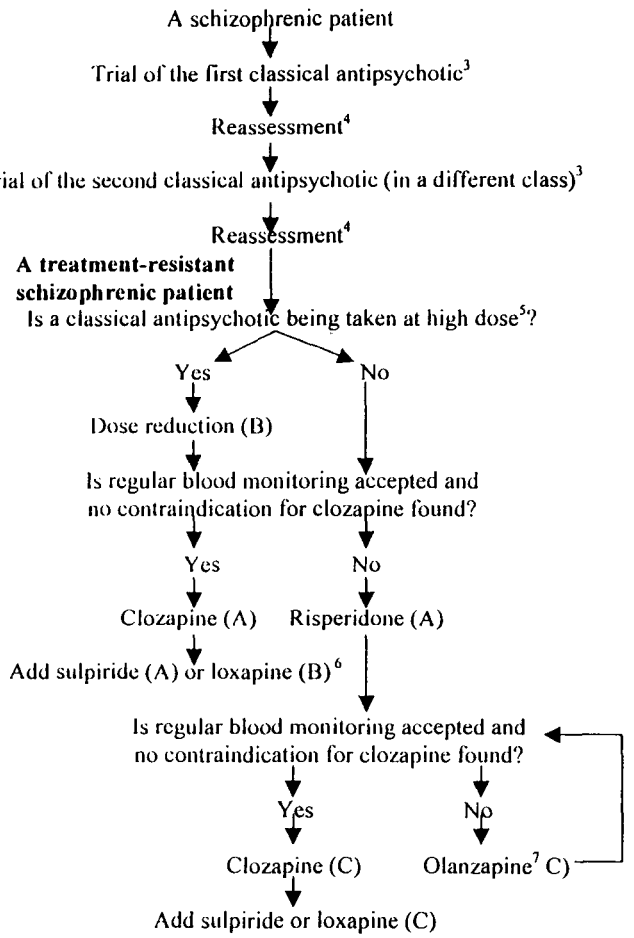

Fig. 1. Flow chart of a pharmacotherapeutic approach[1] for TRS[2].

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 recommedation for other classical antipsychotics.**
7 **Possibly include quetiapine and sertindole if they are available.**

teria. The statements below are recommendations obtained from the reviewed evidence. Fig. 1 shows the flow chart of a pharmacotherapeutic approach for TRS. Table 1 shows the summary of 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 strategy may be only about 9 per cent(8), 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)(9) has been widely used, the definition of an adequate drug trial tends to be less rigorous

Table 1. Summary of the results of trials drawn for establishing 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 20 mg/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 $p < 0.02$
Mowerman & 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 = 0/100	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

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]
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.

recently. According to the review of Conley and Buchanan (1997)[10], 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.

Although some experts suggest the augmentation of lithium or carbamazepine for classical antipsychotic nonresponders[11,12], a dearth of evidence can be found to support those suggestions. In addition, the results of most RCTs suggested that lithium[13-15] and carbamazepine[15] 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[16]. 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 equivalent), a dose reduction strategy may be applied at this stage (B)[17]. 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 [9,18-20]. Second, the benefits of other agents, including risperidone, have been rarely replicated. According to the short-term results of those three large RCTs, the chance of a TRS patient improving by the use of this strategy is about 29–44 per cent. In addition, clozapine is significantly more effective than classical antipsychotics at the pooled nonresponse-rate odd ratio with 95 per cent confidence interval (OR with 95% CI) of 0.30 (0.20–0.45). 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[20].

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 per cent, 0.8 per cent, and 0.03 per cent of 6,316 registered patients developed neutropenia, agranulocytosis, and fatal agranulocytosis, respectively[21].

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 per cent CI of 0.09 with 0.01–0.88, NNT = 2)[22] and loxapine (B)[23]. Switching clo-

zapine to risperidone is not recommended since it may worsen psychotic symptoms (B)[24].

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[25,26], 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)[27]. 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)[28]. However, this strategy should be applied with caution since the condition of some patients may worsen. In addition, at least one to two weeks should be expected for tapering clozapine (C)[29].

Although there is no evidence supporting the use of olanzapine, quetiapine, sertindole, or ziprasidone in a schizophrenic patient who resists both classical antipsychotics and risperidone, giving those atypical antipsychotics may be worth a trial if the TRS patient refuses to have regular blood monitoring or has a contraindication for clozapine (C).

DISCUSSION

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[3], Practice Guideline for the Treatment of Patients with Schizophrenia[4], The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations[5], Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia[6].

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 adverse drug effects. All manageable causes that may impede the treatment response should be examined, for example, adverse drug 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 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.

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.

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[30]. In addition, some experts tend to give an atypical antipsychotic to a schizophrenic patient who resists only one classical antipsychotic[3]. 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)[9]. However, the daily doses suggested in this guideline are in concordance with two comprehensive reviews [31,32]. 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[4-6]. 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 elaborate 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 per cent of the RCTs published in medical journals may not be found by the MEDLINE search[33]. Second, most data included in this guideline are obtained from the studies carried out in western patients and settings. Physicians should be aware of this limitation and may have to make their own judgments in treating an individual patient with TRS in their clinical settings. 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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แนวทางการใช้ยารักษาโรคจิตเภทที่ไม่ตอบสนองต่อการรักษา†

จำลอง ดิษยวณิช, พ.บ., มานิต ศรีสุรภานนท์, พ.บ.*, พิเชฐ อุดมรัตน์, พ.บ.**,*
พริ้มเพรา ดิษยวณิช, Ph.D., ดวงใจ กสานติกุล, พ.บ.***,*
*พงศธร เนตราคม, พ.บ.****, เทียนชัย งามทิพย์วัฒนา, พ.บ.*****,*
*ศรีจันทร์ พรจิราศิลป์, Ph.D.******, พูนศรี รังษีขจี, พ.บ.*******,*
*ไพฑูรย์ สมุทรสินธุ์, พ.บ.********, ปราโมทย์ สุคนิชย์, พ.บ.*********,*
*กิตติวรรณ เทียมแก้ว, พ.บ.**********, ทวีศิลป์ วิษณุโยธิน, พ.บ.************

ผู้นิพนธ์เสนอที่จะพัฒนาแนวทางการใช้ยารักษาโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาที่อิงหลักฐานทางวิชาการ ซึ่งใช้ชื่อว่า "แนวทางการใช้ยารักษาโรคจิตเภทที่ไม่ตอบสนองต่อการรักษา" ผู้นิพนธ์ได้ทำการค้นหาบทความใน MEDLINE (ช่วงปี ค.ศ. 1966 ถึงเดือนธันวาคม ค.ศ. 1998) และได้จำแนกรูปแบบการวิจัยโดยใช้ระบบของ Agency for Health Care Policy and Research (AHCPR) ผู้นิพนธ์ได้จัดระดับของหลักฐานและให้คำแนะนำโดยอาศัยระบบซึ่งปรับปรุงมาจากระบบของ AHCPR บทความจำนวน 163 บทความเข้าได้กับเกณฑ์การนำเข้าสู่ขบวนการทบทวนเอกสาร สำหรับผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาด้วยยารักษาโรคจิตชนิดดั้งเดิมหนึ่งตัว แพทย์ควรเปลี่ยนจากยารักษาโรคจิตชนิดดั้งเดิมดังกล่าวเป็นยารักษาโรคจิตชนิดดั้งเดิมอีกตัวหนึ่งซึ่งอยู่ในกลุ่มที่ต่างกัน ผู้ป่วยโรคจิตเภทที่ไม่ตอบสนองต่อการรักษาอย่างเพียงพอด้วยยารักษาโรคจิตชนิดดั้งเดิมสองตัวควรได้รับการวินิจฉัยว่าเป็นโรคจิตเภทที่ไม่ตอบสนองต่อการรักษา ยา clozapine ควรได้รับการพิจารณาเป็นลำดับแรกในผู้ป่วยชนิดนี้ ส่วนยา risperidone ควรพิจารณาให้ในผู้ป่วยที่ปฏิเสธการติดตามผลเลือดอย่างสม่ำเสมอหรือมีข้อห้ามสำหรับการใช้ยา clozapine แพทย์ผู้รักษาควรใช้แนวทางการรักษานี้ร่วมไปกับแนวทางการรักษาอื่นที่กล่าวถึงภาพรวมของการรักษาผู้ป่วยโรคจิตเภท ผู้นิพนธ์ได้กล่าวถึงการนำแนวทางการรักษาฯ ไปใช้อย่างเหมาะสมและข้อจำกัดของแนวทางการรักษานี้ด้วยเช่นกัน

คำสำคัญ : โรคจิตเภทที่ไม่ตอบสนองต่อการรักษา, การใช้ยารักษา, แนวทาง

จำลอง ดิษยวณิช และคณะ
จดหมายเหตุทางแพทย์ ฯ 2543; 83: 579–589

* ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่, อ. เมือง, จ. เชียงใหม่ 50200
** ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์, อ. หาดใหญ่, จ. สงขลา 90112
*** ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, เขตปทุมวัน, กรุงเทพฯ 10330
**** กองจิตเวชและประสาทวิทยา, คณะแพทยศาสตร์ โรงพยาบาลพระมงกุฎเกล้า, เขตพญาไท, กรุงเทพฯ 10400
***** ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, เขตบางกอกน้อย, กรุงเทพฯ 10700
****** ภาควิชาเภสัชวิทยา, คณะเภสัชศาสตร์, มหาวิทยาลัยมหิดล, เขตพญาไท, กรุงเทพฯ 10400
******* ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, อ. เมือง, จ. ขอนแก่น 40002
******** โรงพยาบาลศรีธัญญา, อ. เมือง, จ. นนทบุรี 11000
********* ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, เขตพญาไท, กรุงเทพฯ 10400
********** โรงพยาบาลสวนปรุง, อ. เมือง, จ. เชียงใหม่ 50200
*********** โรงพยาบาลสมเด็จเจ้าพระยา, เขตคลองสาน, กรุงเทพฯ 10600

† โครงการนี้เป็นกิจกรรมทางวิชาการของราชวิทยาลัยจิตแพทย์แห่งประเทศไทยและได้รับทุนอุดหนุนจากสถาบันวิจัยระบบสาธารณสุข
† ความเห็นและข้อเสนอแนะในเอกสารนี้เป็นของคณะทำงานฯ เท่านั้น มิใช่เป็นความเห็นขององค์กรทั้งสอง
† ฉบับเต็มของแนวทางการรักษานี้สามารถดูได้ที่ http://go.to/ptrsguideline