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- Title: Development of a Guideline for Antipsychotic-induced Hyperprolactinemia in Korea Using the ADAPTE Process
- Running Title: Development of Guidelines for Antipsychotic Drug-induced Hyperprolactinemia
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ABSTRACT

Objective: To develop an evidence-based guideline for the diagnosis and treatment of antipsychotic-induced hyperprolactinemia by adapting existing high-quality clinical guidelines with a view to improve the clinical symptoms and long-term quality of life of patients by providing appropriate management.

Methods: This guideline was developed according to the ADAPTE methodology. The adaptation process included determining key health questions, systematically searching and screening guidelines, evaluating the quality and contents of these guidelines, deriving recommendations for key questions, and performing a peer review. The selection criteria for the guideline search were (1) evidence-based guidelines, (2) published within the last 5 years, and (3) written in English or Korean.

Results: After evaluating the quality and content, we finally selected three guidelines for adaptation. The final output of the development process was 25 recommendations for 10 key questions. We adopted the Agency for Health Research Quality methodology and presented the level of evidence from levels I to IV. In addition, we defined the recommendation grades from grade A (strongly recommended) to D (no recommendation) based on the level of evidence and clinical significance of the recommendation.

Conclusion: The development and dissemination of the adapted guideline is expected to increase the certainty of medical decision making and improve the quality of medical care. Further studies on the effectiveness and applicability of the developed guideline are necessary.

Key words: Guideline; Hyperprolactinemia; Antipsychotic Agent; Evidence-based Practice

INTRODUCTION

Hyperprolactinemia can be caused by several physiological and pathological conditions. Physiologically, pregnancy, lactation, sexual intercourse, physical exertion, sleep, and stress can increase prolactin levels [1]. Pathologically, tumors of the pituitary gland and hypothalamus, hypothyroidism, liver cirrhosis, chronic renal failure, and polycystic ovary syndrome can induce hyperprolactinemia [2]. However, the most frequent cause of non-physiological hyperprolactinemia is drug exposure [3].Antipsychotic drugs are a major cause of hyperprolactinemia [2], with 50–70% of patients who take antipsychotic drugs developing hyperprolactinemia [4-6].

Antipsychotics such as risperidone, paliperidone, amisulpride, and first-generation antipsychotics block D2 dopamine receptors and can cause hyperprolactinemia by interfering with dopamine-induced suppression of prolactin secretion [7]. Since dopamine has an inhibitory effect on prolactin secretion, dopamine inhibition by antipsychotics in the tuberoinfundibular pathway of the hypothalamus increases serum prolactin levels [8]. Although there is inconsistency in reported criteria, hyperprolactinemia is generally defined as serum prolactin levels >20 ng/mL in men and >25 ng/mL in women [7, 9-11]. Hyperprolactinemia severity can be categorized as mild (≤50 ng/mL), moderate (51–100 ng/mL), and severe (≥101 ng/mL) [9]. Hyperprolactinemia caused by antipsychotics is usually moderate to severe rather than mild [8]. Pituitary tumors can cause higher prolactin levels than those seen in drug-induced hyperprolactinemia; however, with some drugs, such as risperidone, prolactin levels can exceed 200 ng/mL [12, 13].

Hyperprolactinemia due to antipsychotics can manifest clinical signs and symptoms in

various body organs. Symptoms that appear earlier include galactorrhea, gynecomastia, irregular menstruation, amenorrhea, and sexual dysfunction [1, 14]. Long-term side effects include infertility, early menopause, osteoporosis, increased cancer risk (e.g., breast, ovarian, and endometrial cancer), increased cardiovascular risk, and cognitive decline [15]. These side effects may appear due to direct effects on prolactin receptors expressed in the breast, endometrium, ovary, testis, brain, pancreas, lymphocytes, adipocytes, and endothelial cells, as well as indirect effects related to lowered sex steroid levels [12]. Increased prolactin levels inhibit the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, resulting in low gonadal steroid levels and hypogonadism [15].

Physicians should monitor and manage the risk of these side effects in patients taking antipsychotics. However, in Korea, there remains no evidence-based agreement regarding the screening criteria for hyperprolactinemia before and after antipsychotic drug treatment or the necessary examinations or treatments when hyperprolactinemia is suspected. Many patients currently taking antipsychotic drugs do not receive adequate education and/or monitoring for hyperprolactinemia. Thus, they often visit obstetrics and gynecology, urology, and internal medicine specialists and undergo unnecessary tests and treatments, which increase medical expenses.

Although hyperprolactinemia is a common side effect of antipsychotics in clinical practice, no evidence-based guidelines exist to provide specific and practical guidance in Korea [4-6]. Similarly, few recent guidelines for antipsychotic-induced hyperprolactinemia have been published globally within the last 5 years. Moreover, some of these guidelines did not focus on hyperprolactinemia but rather provided general guidance for patients with schizophrenia and

bipolar disorder, as well as gynecological patients, with only a small portion of the text containing recommendations for the management of hyperprolactinemia [16-20]. It was challenging to identify evidence-based clinical guidelines that focused on antipsychotic-induced hyperprolactinemia and included specific recommendations for pre-evaluation, diagnosis, monitoring, examination, treatment, and education while also providing evidence to support each recommendation. Although some authors have attempted to create new guidelines by analyzing existing guidelines through systematic literature review, they relied on expert consensus rather than scientifically analyzing the quality and content of each guideline [21, 22]. A detailed description of the rationale for reaching the consensus is also lacking [21, 22]. Therefore, it is essential to develop an evidence-based clinical guideline for antipsychotic-induced hyperprolactinemia considering the domestic clinical practice environment.

There are two methods of developing guidelines—directly developing new guidelines (de novo) or adapting pre-existing guidelines. Since significant resources are required and there is a lack of accumulated evidence from domestic studies for de novo development, Korea mainly refines foreign guidelines to fit the domestic situation. This study aimed to develop an evidence-based clinical guideline for the diagnosis, monitoring, evaluation, and treatment of antipsychotic-induced hyperprolactinemia by adapting existing high-quality guidelines.

METHODS

This methodological study described the process of screening and adapting pre-existing guidelines for antipsychotic-induced hyperprolactinemia according to the ADAPTE process

[23]. The ADAPTE Collaboration, an international interdisciplinary organization, was formed to establish standard procedures and methodologies for the process of adapting medical guidelines. They proposed the ADAPTE process as a systematic approach that uses or modifies clinical guidelines developed for specific cultural contexts in other medical situations [23]. The ADAPTE process is illustrated in Figure 1. The institutional review board of Chung-Ang University Hospital approved the study protocol (Approval number: 2103-002-195356).

Phase 1: Set-up

First, an organizing committee was established to manage the guideline adaptation process. The committee was responsible for defining the guideline topic, forming a working committee, developing an adaptation plan, reviewing the recommendations, and approving the draft guideline. In the planning stage, the organizing committee set the guideline topic as the "diagnosis, examination, and treatment of antipsychotic-induced hyperprolactinemia," checked the feasibility of accommodation development, and identified the necessary resources related to the guideline. As there were existing overseas guidelines for antipsychotic-induced hyperprolactinemia, the committee decided to adapt these existing guidelines instead of developing new guidelines. The organizing committee then formed the working committee to identify clinical guidelines, evaluate the quality and timeliness of the guidelines, and draft recommendations and the guideline. The organizing and working committees were combined in the development committee. The development committee signed a statement of interest before the development of the guidelines. The declaration of interest included involvement in the development or approval process of the guideline under review and whether it had commercial relevance.

Phase 2: Adaptation

Scope and purpose

The scope of this guideline was described using the Population, Intervention, Professionals, Outcomes, Healthcare setting (PIPOH) tool (Table 1). The population group was limited to adult patients aged ≥19 years with antipsychotic-induced hyperprolactinemia. The scope of the guideline broadly included the diagnosis, monitoring, evaluation, treatment, and education of hyperprolactinemia occurring due to the use of antipsychotic drugs. The target users were psychiatric specialists, obstetricians and gynecologists, urologists, endocrinologists, family medicine specialists, and general practitioners. The purpose of the guidelines was to improve patient symptoms and quality of life, reduce long-term harm, and improve the appropriateness of medical practice. The key health questions were defined according to the scope of the guidelines. The final recommendations were made based on these key questions.

Search and screening

The search terms were (hyperprolactinemia OR prolactin) AND (antipsychotic agents OR antipsychotic OR neuroleptic OR drug therapy OR medication OR iatrogenic) AND (guideline OR recommendation OR consensus). A literature search expert searched both overseas and domestic databases. The search results were limited to results in English or Korean and materials published after 2016. The overseas databases included PubMed, Embase, Cochrane, Web of Science, and Scopus. We additionally searched for “hyperprolactinemia AND guideline” or “hyperprolactinemia” on sites that provide overseas guidelines such as the National Institute for Health and Care Excellence but did not find any data from after 2016. The domestic

databases included the Korean Studies Information Service System, DBpia, Science ON, Korea Citation Index, KMBASE, and Research Information Sharing Service. When the search target was limited to guidelines, no domestic data were found. The search results of an expanded search scope to "hyperprolactinemia (or hyperprolactinemia) AND antipsychotic drugs" or "hyperprolactinemia (or hyperprolactinemia)" included data other than clinical guidelines. The Korean Clinical Practice Guidelines Center contained no guidelines related to "hyperprolactinemia." The inclusion criteria were evidence-based guidelines, information on the level of evidence and strength of recommendations, guidelines issued within the last 5 years, and guidelines written in English or Korean. The exclusion criteria were guidelines published by a single author rather than multiple expert groups, guidelines published without references, and guidelines for children and adolescents only.

Assessment

The quality of the guidelines was evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool [24]. This tool consists of six domains and 23 items: 1) scope and purpose (items 1–3), 2) stakeholder engagement (items 4–7), 3) rigor of development (items 8–14), 4) clarity and expression of language (items 15–18), 5) applicability (items 19–21), and 6) editorial independence (items 22–23). Five working committee members evaluated the 23 items and scored them on a Likert scale ranging from 1 to 7. The scores for the six domains were independently calculated and used as a reference for comparing the guidelines. The guidelines selected through AGREE II were evaluated in terms of currency, content, and acceptability/applicability. To evaluate the updated guidelines, we reviewed the date of publication or the date of the last search for the included evidence. To evaluate the

guideline contents, we checked whether they included descriptions related to the health questions of the new guideline in the contents of the existing guidelines. To evaluate the acceptability and applicability of the guidelines, we considered the Korean culture and medical system.

Decision and selection

The working committee members extracted recommendations for key questions from the selected guidelines and drafted recommendations. After a review of the evidence on the recommendations, a preliminary meeting was conducted to discuss the clarity of recommendations and their acceptability and applicability and determine which recommendations would and would not be accepted. A formal consensus using the nominal group technique (NGT) was implemented to accept recommendations that reached a consensus >70%. In addition, among the recommendations to be accepted, amendments were made if needed. These amendments were proposed through informal consensus and confirmed through formal consensus using NGT. If >70% agreed, the amendment was confirmed. The development committee shared the final recommendations and supporting data. As in the preliminary meeting, a formal consensus using NGT was implemented for each recommendation; when >70% consensus was reached, it was confirmed as a final recommendation.

Guideline draft

The draft of the guideline consisted of the following: 1) introduction, 2) method for guideline development, 3) clinical guideline, and 4) appendices. The background, scope, and

purpose of the guideline are described in the introduction. The method for guideline development described the committee composition, selection of key questions, and the search and evaluation process. The clinical guideline included recommendations for the key questions. It also included the level of evidence, strength of the recommendation, summary of the evidence, and domestic acceptance and applicability of each recommendation. We applied the Agency for Health Research Quality methodology and presented the level of evidence from level I to IV. The recommendation grades were categorized from grade A (strongly recommended) to D (no recommendation) based on the level of evidence and the clinical significance of the recommendation. The appendix included the results of the declaration of interest, the evaluation results of the searched guidelines, a summary of recommendations, and an algorithm for antipsychotic-induced hyperprolactinemia. The development committee reviewed and approved the contents.

Phase 3: Finalization

External review

We received feedback on the guideline from target users. The reviewers comprised seven psychiatrists, one family medicine specialist, one obstetrician-gynecologist, one urologist, and one endocrinologist. Drafts of the guidelines were emailed for external review using the Delphi method. The Delphi method is a consensus methodology developed by the RAND group and is conducted with a survey and feedback on the results without a face-to-face meeting with experts [25]. The experts rated their degree of agreement with each recommendation on a nine-point Likert scale ranging from “strongly agree” (9 points) to “strongly disagree” (1 point). If >70% of the reviewers responded with a score of 7–9, a

consensus was reached on the recommendation. If a consensus was not reached in the first Delphi round, an additional Delphi round was held.

Aftercare planning

If new evidence is established with accumulating research on the diagnosis, monitoring, evaluation, and treatment of antipsychotic-induced hyperprolactinemia, the guidelines will be revised.

RESULTS

Phase 1: Set-up

Thirteen members, recommended by the Korean Psychosomatic Society, comprised the organizing committee. The working committee comprised five psychiatrists and one methodology expert. All members signed the declaration of interest documents and had no conflicts of interest.

Phase 2: Adaptation

Scope and purpose

A total of ten key health questions were derived related to the scope of the guideline (Table 2).

Search and screen

The screening process for medical guidelines is shown in the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2).

Assessment

After reviewing 379 foreign and 7 domestic papers identified through the systematic evidence search process, we finally selected three guidelines for quality evaluation using AGREE II. The included guidelines were: #1, "Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology" [20]; #2, "Spanish consensus on the risks and detection of antipsychotic drug-related hyperprolactinemia" [15]; and #3, "Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics" [26]. Guideline #1 is not a guideline only for hyperprolactinemia caused by antipsychotics, but is a broad guideline for the use of antipsychotic drugs in patients with schizophrenia; thus, it was difficult to find specific explanations and descriptions for the key questions of the guideline to be developed in the present study. However, it was recommended for use after revision as it contained recommendations corresponding to the key question for pre-evaluation. Guideline #2 included recommendations appropriate to the key questions and was evaluated as a high-quality clinical guideline with a scientific design and clear explanations. Since it was primarily associated with diagnosis and evaluation of antipsychotic-induced hyperprolactinemia, treatment was only described briefly, which is a disadvantage of this guideline. Guideline #3 was developed by the developer of guideline #2 and included evidence-based recommendations appropriate to key questions regarding the treatment of antipsychotic-induced hyperprolactinemia. Although the quality level was evaluated as high overall, the "rigor of development" score was slightly lower than that of guideline #2 due to insufficient

explanation of the guideline development process. Therefore, the working committee decided to adopt guideline #1 with some revisions, as well as guidelines #2 and #3, to complement each other in areas lacking appropriate recommendations for the key questions. We evaluated whether the guidelines included the latest evidence but found no new evidence to revise the level of evidence or strength of recommendations of the existing guidelines.

Decision and Selection

The working committee drafted recommendations corresponding to ten key questions by referring to the recommendations of the selected guidelines. After exclusion of the recommendations, which could not be accepted using the NGT method, the recommendations, which could be accepted were revised according to their acceptability and applicability in Korea. The recommendations that were excluded because of not achieving more than 70% agreement were mainly about the screening and treatment for osteoporosis risk associated with hyperprolactinemia. The recommendation in guideline #2 regarding "using FRAX (fracture risk assessment tool) to evaluate the risk of osteoporotic fracture in men who are ≥ 50 years of age and postmenopausal women prior to prescribing antipsychotic drugs" was excluded. Since long-term exposure to antipsychotics increases fracture risk, it is not cost-effective to evaluate fracture risk before starting treatment [27-29]. Therefore, we considered that enquiring about menopause status and history of fractures or osteoporosis before prescribing antipsychotic drugs was a practical way to identify groups at high risk for fractures, and we accepted recommendations containing such information. Additionally, bone density testing, a kind of X-ray, is mainly used rather than FRAX to assess the risk of osteoporosis in clinical practice in Korea. We accepted the recommendation to perform a bone density test to evaluate the risk of

fracture and osteoporosis in patients exposed to antipsychotics for more than 5 years. The recommendation in guideline #2 regarding “measuring vitamin D levels at baseline and every 6 months if hyperprolactinemia is present” was also excluded. The increased risk of osteoporosis in antipsychotic-induced hyperprolactinemia is a complication that is caused by decreased levels of sex hormones and is not due to a decrease in vitamin D levels [28]. Since vitamin D levels are not predictive of osteoporosis, they were excluded from the recommendations. Among the treatment recommendations, the recommendation in guideline #3, “if amenorrhea persists for more than 3 months, a change of antipsychotics should be considered because of the risk of osteoporosis” was excluded. The risk of osteoporosis increases after long-term exposure to antipsychotic drugs (more than 5 years) and only 3 months of amenorrhea was not considered a sufficient period to consider changing antipsychotic drugs due to the risk of osteoporosis [27-29]. For the same reason, the recommendation of “In the case of amenorrhea persists for more than 6 months, if treatment cannot be changed, oral contraceptives are recommended to prevent osteoporosis” was also excluded. The recommendation in guideline #2, “In the presence of hyperprolactinemia, the level of gonadotropin should be measured at baseline and every 6 months to rule out hypogonadism,” was excluded because the gonadotropin test is difficult to measure at local clinics and regular measurement is not cost-effective.

The recommendations for serum prolactin testing were revised according to accessibility, applicability, and economic efficiency of local medical institutions in Korea. While the recommendation for serum prolactin testing at baseline, before the initiation of antipsychotic treatment was accepted, the recommendation grade was downgraded from A to

C. The recommendation to routinely perform serum prolactin tests 3 months after treatment with antipsychotic drugs was modified to check for the side effects of hyperprolactinemia 3 months after starting treatment, and to perform serum prolactin tests in people with suspected side effects. The recommendation in guideline #1, "If there is uncertainty about the interpretation of prolactin levels and their effect on fertility, the opinion of an endocrinologist should be sought," was amended to "the opinion of an endocrinologist or obstetrician-gynecologist should be sought" to reflect the reality of practice, in which obstetricians are often asked for advice on fertility. Guideline #2 recommended that women taking antipsychotics should be monitored for changes in the breast and menstrual cycles at least every 3 months. Since 3 months is insufficient to evaluate the regularity of and changes in the menstrual cycle, including women with long menstrual cycles, we modified it to examine changes in the breast and menstrual cycle at least every 3 to 6 months. The strength of the recommendation from guideline #2 regarding the use of dopamine receptor agonists for the treatment of hyperprolactinemia was revised from grade B to C. While the efficacy and safety of dopamine receptor agonists have been confirmed in studies with a high level of evidence, such as randomized trials and meta-analyses [30-32], the grade was downgraded because studies have reported side effects, such as exacerbation of psychosis, abnormal movement, and cardiac complications, related to the use of dopamine agonists [33-36].

A total of 25 recommendations were prepared by the working committee and reviewed by the development committee. A consensus exceeding 70% was reached for all recommendations using the NGT method.

Phase 3: Finalization

After an external review through three Delphi rounds, the final recommendation was confirmed. All recommendations reached a consensus of more than 70% in the third round. The final result of the development process provided 25 recommendations for ten key questions.

DISCUSSION

This methodological study described the process of applying foreign guidelines to the Korean clinical environment to develop an evidence-based guideline for the management of antipsychotic-induced hyperprolactinemia. It aims to improve patient symptoms and quality of life, reduce long-term harm, and improve the appropriateness of medical practice. The health questions of the guideline cover pre-assessment, diagnosis, monitoring, evaluation, treatment, and education of antipsychotic-induced hyperprolactinemia.

This study aimed to develop a guideline that is reliable and helpful in clinical practice in Korea using the ADAPTE process, which is a step-by-step and standard adaptation method to develop clinical guidelines. For the systematic search process, we tried to select high-quality medical guidelines based on the level of evidence and strength of the recommendations. In addition, the guidelines included in the adaptation were scientifically compared and evaluated using tools such as AGREE. Domestic acceptance and applicability were reflected by modifying existing guidelines through the official consensus process of the development committee. The revisions reflecting the domestic situation were described in the “domestic acceptability and applicability” section of each recommendation. An external panel survey was used to identify user requirements and the rate of agreement with the guideline to increase their

practical use. In addition, we described the rational decision-making process in detail to increase the reliability of the developed recommendations. The “Evidence-based guideline for antipsychotic-induced hyperprolactinemia” resulting from the above development process provides clear recommendations for specific clinical questions applicable in actual practice and includes the level of evidence, a summary of the evidence, and the strength of each recommendation. A summary of the recommendations and an algorithm for antipsychotic-induced hyperprolactinemia, which are available in the appendix of this paper, have been proposed to enhance the implementation of the developed guideline.

This study had some limitations. First, evidence is lacking regarding the pre-evaluation of and education regarding antipsychotic-induced hyperprolactinemia. Therefore, the recommendations regarding these topics were made based on low-level evidence such as reports published by the expert committee, clinical experience of experts, evidence obtained from case studies, or the consensus of the development committee. Second, although guidelines published within the last 5 years were selected, these guidelines included evidence published 10 to 15 years ago. We tried to compensate for these shortcomings by reflecting the contents of recently published evidence through up-to-date evaluations. Third, the inclusion of guidelines published over the last 10 years could have allowed the evaluation of even higher-quality overseas guidelines as targets for adaptation. However, in that case, the up-to-date guidelines would have deteriorated, and unnecessary time and manpower would have been required to search for and evaluate data. Fourth, evidence and explanations regarding the economic cost-effectiveness of each recommendation were insufficient.

We developed evidence-based guidelines primarily for domestic use. However, since

evidence-based guidelines for antipsychotic-induced hyperprolactinemia are lacking abroad, publishing an English translation of the developed guidelines would be beneficial. Further studies are needed to assess the effectiveness and applicability of the developed guidelines. It will be necessary in the future to develop clinical guidelines reinforced with the latest evidence for the pre-evaluation and education of antipsychotic-induced hyperprolactinemia and the economic efficiency of the recommendations.

Conflicts of Interest

The authors do not have any conflict of interest to disclose.

Author contributions

Conceptualization: Kim SM. Data acquisition: Kang WS, Jeon HJ, Jang S-H, and Hong J. Formal analysis: Kim HR and Kim SM. Funding: Kim SM, Hong J, and Jeong J-H, Supervision: Jeong J-H. Writing—original draft: Kim HR. Writing—review and editing: Kim SM and Jon D-I. Approval of the final manuscript: All authors.

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Figure Legends

Figure 1. The ADAPTE process

Figure 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Table 1. Population, Intervention, Professionals, Outcomes, and Health settings (PIPOH)

PIPOH	Category	Contents
Population	Adult patients ≥19 years of age with antipsychotic-induced hyperprolactinemia	
Intervention	Diagnosis	Serum prolactin level, clinical symptoms, differential diagnosis
	Monitoring	Serum prolactin level, clinical symptoms
	Evaluation	Neuroimaging, serum gonadal hormone test, bone densitometry
	Management	Pharmacological and non-pharmacological treatment, education
Professions	General practitioners and related specialists (psychiatrists, gynecologists, urologists, endocrinologists, family medicine specialists, etc.).	
Outcome	Patient outcome	Symptom control, improvement of quality of life, reduction of long-term harm
	System outcome	Improvement of the appropriateness of diagnosis and treatment
Healthcare setting	Medical institutions	Primary medical institutions, outpatient and inpatient treatment institutions

Table 2. A list of health questions

1 Pre-evaluation of antipsychotic-induced hyperprolactinemia
1.1 Should basal prolactin levels be measured before initiating antipsychotic therapy?
2 Diagnosis of antipsychotic-induced hyperprolactinemia
2.1 What is the normal range of serum prolactin levels following antipsychotic treatment?
2.2 What are the main clinical symptoms of hyperprolactinemia?
3 Monitoring of antipsychotic-induced hyperprolactinemia
3.1 How often (at what interval) should follow-up serum prolactin levels be measured in patients receiving antipsychotics?
3.2 What tests should be performed regularly to check for symptoms of hyperprolactinemia in patients receiving antipsychotics?
4 Examination for antipsychotic-induced hyperprolactinemia
4.1 What tests should be performed for a patient receiving antipsychotics and having hyperprolactinemia with mildly elevated serum prolactin levels?
4.2 What tests should be performed if moderate or severe hyperprolactinemia is found in patients receiving antipsychotics or if there is prolonged hyperprolactinemia?
5 Treatment of antipsychotic-induced hyperprolactinemia
5.1 What treatment should be provided when antipsychotic-induced hyperprolactinemia

is detected with mild and asymptomatic elevation of serum prolactin level?

5.2 What treatment should be provided when antipsychotic-induced hyperprolactinemia is detected with moderate or severe hyperprolactinemia or clinical symptoms?

6 Education on antipsychotic-induced hyperprolactinemia

6.1 What should be included in the education of patients with hyperprolactinemia receiving antipsychotics?

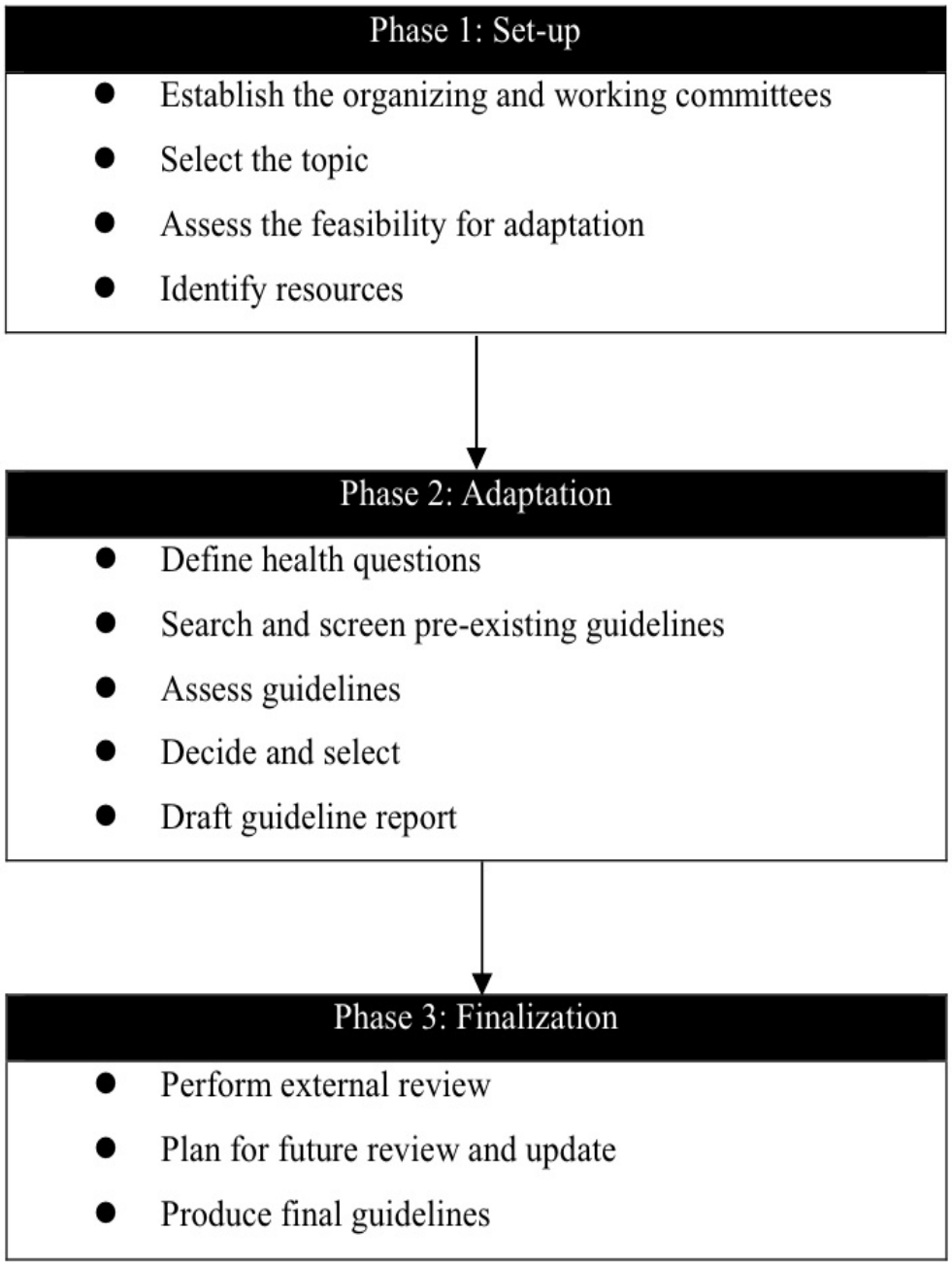

Fig. 1. The ADAPTE process

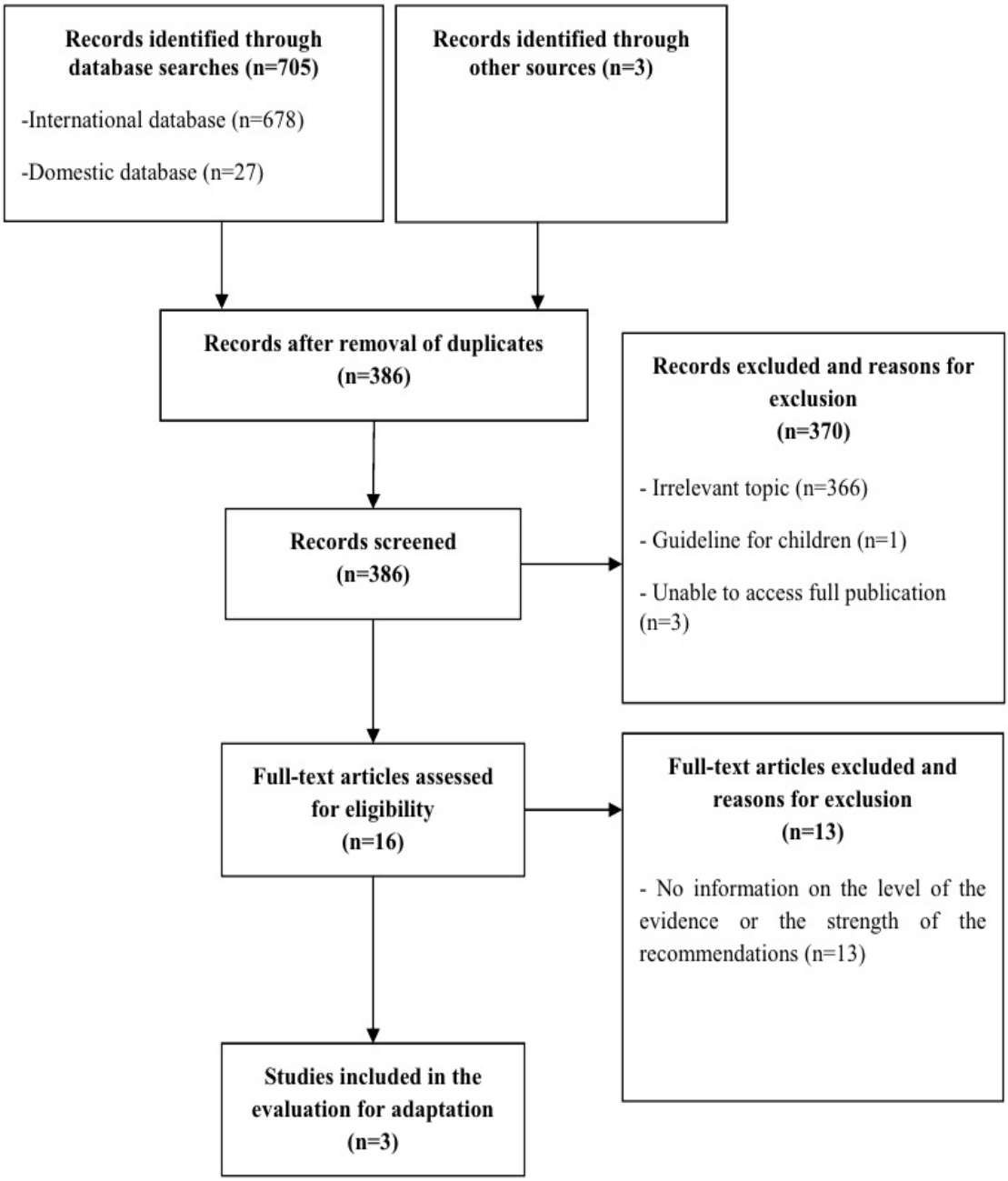

Fig. 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram