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The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes and intervention strategies

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Abstract

In many developing countries, people with epilepsy do not receive appropriate treatment for their condition, a phenomenon called the treatment gap (TG). We carried out a systematic review to investigate the magnitude, causes and intervention strategies to improve outcomes in developing countries. We systematically searched MEDLINE, EMBASE and PsycINFO databases, supplemented by a hand search of references in the key papers. The degree of heterogeneity and a pooled TG estimate were determined using meta-analysis techniques. The estimates were further stratified by continent and location of study (urban, rural). Twenty-seven studies met the inclusion criteria: twelve from Africa, nine from Asia and six from Latin America. We observed a high degree of heterogeneity and inconsistency between studies. The overall estimate of the TG was 56/100 (95% CI: 31.1-100.0). The variation in estimates could possibly be explained by non-uniform TG estimation methods and the diverse study populations, among other factors. The TG was mainly attributed to inadequate skilled manpower, cost of treatment, cultural beliefs and unavailability of anti-epileptic drugs (AEDs). These factors have been addressed using different intervention strategies for instance education and supply of AEDs. Future research should estimate the TG coherently and develop sustainable interventions that will address the causes.

Keywords

Epilepsy; treatment gap; anti-epileptic drugs; adherence; interventions; developing countries

Introduction

The Epilepsy treatment gap

Epilepsy is the most common chronic neurological disorder, affecting approximately 50 million people worldwide, of whom 40 million are estimated to live in developing countries[1] (WHO, 2004). Several studies have reported that over 90% of people with

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We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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epilepsy (PWE) in developing countries do not receive appropriate treatment for their condition, a phenomenon known as the treatment gap (TG) (Scott *et al.*, 2001; Diop *et al.*, 2003; Diop *et al.*, 2005; Shorvon & Farmer, 1988). However, none of the studies provide a confidence interval, suggesting that the estimate is not data driven. The TG is defined as the number of people with active epilepsy not on treatment (diagnostic and therapeutic) or on inadequate treatment, expressed as a percentage of the total number with active epilepsy (Kale, 2002; Meinardi *et al.*, 2001). The epilepsy treatment gap (ETG) has a broader definition to include the influence of epilepsy on mental and social well being (Meinardi *et al.*, 2001). For the purpose of this review, active epilepsy is defined as having at least one unprovoked seizure in the last 5 years. The TG has been estimated by the direct method during prevalence studies, and indirectly from the amount of anti-epileptic drugs (AEDs) consumed in the country and the number of people with active epilepsy (Kale, 2002). The gap is reported to be influenced by various factors, including lack of access to or knowledge of AEDs, poverty, cultural beliefs, stigma, poor health delivery infrastructure and shortage of trained professionals (Scott *et al.*, 2001; Meinardi *et al.*, 2001).

The Global Campaign Against Epilepsy, a partnership between the World Health Organization (WHO), International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) was launched in 1997 to bring epilepsy “out of the shadows” by addressing some of the factors outlined above (Sander, 2002; Diop *et al.*, 2003). In 2002, the Global Campaign entered its second phase and several demonstration projects were set up in various countries, to reduce the TG and the physical, economic and social burden of epilepsy through community-level interventions (Sander, 2002; Li *et al.*, 2007). Despite this concerted effort by different stakeholders, there are no systematic reviews on the magnitude, causes or intervention strategies to improve the outcomes in developing countries. Therefore we conducted a systematic review of the literature on the TG to answer the following questions:

1. What is the magnitude of the TG in developing countries?
2. What are the factors responsible for the TG in developing countries?
3. What interventions have been implemented to address causes of the TG?

Methods

Data sources and search strategy

A literature search was carried out using three databases: MEDLINE (1966 – 6/2007), EMBASE (1980 – 6/2007) and PsycINFO (1887 –6/2007) using a combined text word and medical subject headings (MeSH) to identify relevant papers (Appendix 1). Additional articles were identified by searching references cited in the key papers. The strategy was developed by breaking the review question into its elemental facets: exposure, outcome, population, publication language and keywords according to the recommendations of the National Health Service Centre for Reviews and Dissemination (K.S Khan *et al.*, 2001) (Appendix 1). Publication language was left open to ascertain how many studies were available in languages other than English.

[1]Developing countries were defined according to the World Bank classification for low and upper middle income as a Gross National Income per capita of less than $11, 115 (http://www.worldbank.org).

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Study Selection

The online abstracts of studies identified from the database search were reviewed and reprints of potential eligible studies obtained. Studies meeting one of the following criteria were chosen for more detailed review:

1. Cross-sectional studies that provide the prevalence of the TG, or studies using the indirect method to estimate the gap
2. Qualitative or observational studies that identify potential causes of the TG
3. Interventions to address some of the attributed causes of the TG: prospective cohort or those that have used randomized control or pre-post designs and focused on either education or supply of drugs.

Studies excluded

1. Epilepsy prevalence studies that did not estimate the TG
2. Studies reported in languages other than English
3. Reviews
4. Editorials, letters or reports
5. Studies conducted in developed countries
6. Studies that reported same results in different papers.

Data extraction

Data were extracted using a proforma designed for the review. The first reviewer extracted all the data and the fourth reviewer re-extracted data from a sample of half of the studies. The studies were organized into three broad categories: those on magnitude, attributed causes and interventions. Information from each study was then obtained on author, year of publication, country, study design, sample size, ascertainment method, length of study, age of participants and outcome. We extracted data on magnitude of the TG and calculated a 95% confidence interval (95% CI) around the estimates. We further stratified the TG estimates by continent and location of study (urban, rural). All data were entered in an Excel spreadsheet and transferred to STATA version 9.2 for analysis.

Analysis

The 95% CI for the TG estimates were calculated and heterogeneity investigated. The TG prevalence estimates were transformed to logits (log (p/1-p)) to improve their statistical properties and later back-transformed to prevalences and expressed as percentages. For further analysis, the data was stratified by continent and location of the study. Attributed causes of the TG were listed and compared across continents using descriptive statistics but such comparison was not performed for the interventions because they measured different outcomes and few provided numerical estimates.

Description of heterogeneity and summary estimates

We used a forest plot (Lewis & Clarke, 2001) to visualize the extent of heterogeneity among the studies that investigated the magnitude of the TG. The standard test for heterogeneity, the Cochrane χ^2 test, was used to examine the null hypothesis of homogeneity. We used a method that quantifies inconsistency across studies, thus assessing its impact on the meta-analysis. This statistic is $I^2 = ((Q - df)/Q) \times 100\%$, where Q is the chi-squared statistic and df is its degrees of freedom (Higgins & Thompson, 2002; Higgins, 2003). I^2 describes the

percentage of the variability in estimates that is due to true heterogeneity (true differences in TG prevalence) and a value greater than 50% was considered substantial heterogeneity.

The mean TG prevalence and its confidence intervals were derived from random effects meta-analysis, an analytical approach used when heterogeneity cannot be readily explained. This assumes that the outcomes being estimated in the different studies are not identical, but follow a normal distribution, allowing for variation between studies. However, the usual confidence interval of mean in the random effects model does not take into account the between study variance and so can be narrow where there is substantial heterogeneity. We therefore calculated the 95% CI for the true TG prevalence as the mean of logits ± 1.96ℓ, where ℓ is the among study standard deviation (Goodman, 1989).

Assessment of methodological quality

The studies were appraised by two independent reviewers based on the criteria outlined in a critical appraisal guide (Crombie, 1996) and guidelines on how to appraise a paper (Greenhalgh, 2001). The relevant methodological aspects were identified and assessed individually for each study. The studies were then rated as good, average or poor as outlined in appendix 2. We did not use a composite numerical score to reflect overall methodological quality because there is no gold standard for the "true" methodological quality and such scores are probably neither valid nor reliable in practice (Greenhalgh, 2001). Empirical evidence and theoretical considerations suggest that although summary quality scores may in some circumstances provide a useful overall assessment, they should not generally be used to assess the quality of studies in systematic reviews because different scales give divergent scores and rankings on one study (Juni *et al.*, 1999; Greenland, 1994).

Results

The electronic search produced 130 references. A hand search of references cited in the key papers identified fifteen additional papers (Appendix 3). These papers were obtained and reviewed and the majority were subsequently excluded because they did not meet the review criteria: they were review articles (n=20), editorials or letters (n=12), reports (n=20), not in English (n=2), prevalence studies that did not estimate the TG (n=19), trials of AEDs (n=10), economic evaluation studies (n=5), studies in developed countries (n=28) or studies reporting the same results in different papers (n=2)

Twenty seven studies fulfilled the inclusion criteria. Twelve (44%) were prevalence studies that measured the TG, eight (30%) identified attributed causes of the TG and the remaining seven (26%) reported the effect of interventions designed to address the attributed causes of the TG. Twelve (45%) of the studies were conducted in Africa, nine (33%) in Asia, and six (22%) in Latin America.

Magnitude of the treatment gap

Out of the twelve studies identified, six (50%) were conducted in Latin America (Mendizabal & Salguero, 1996; Nicoletti *et al.*, 1999; Noronha *et al.*, 2004; Medina *et al.*, 2005; Somoza *et al.*, 2005; Noronha *et al.*, 2007, three (25%) in Africa (Coleman *et al.*, 2002; Ndoye *et al.*, 2005; Dent *et al.*, 2005) and three (25%) in Asia (Aziz *et al.*, 1997; Radhakrishnan *et al.*, 2000; Wang *et al.*, 2003). The majority, eleven (92%) were population-based cross-sectional surveys, while one (8%) used indirect method to estimate the gap. There was wide variability in the TG estimates among the studies that provided its magnitude (Fig 1). The Cochrane χ^2 statistic and measure of inconsistency were large ($Q = 1331.5$, $df = 13$, $p < 0.0001$; $I^2 = 99\%$), suggesting substantial variation among the studies that was beyond sampling variation. The random effects mean of the TG prevalence for all

of the studies was 56.0/100 (95% CI for true prevalence: 31.1-100.0). When stratified by continent, the random effects mean of the TG prevalence for Latin America was 55.4/100 (95% CI: 39.0 -78.6), Asia 64.0/100 (95% CI: 24.3-100.0) while that of Africa was 49.0/100 (95% CI: 14.0-100.0). The mean of the TG prevalence for urban settings was estimated at 46.8/100 (95% CI: 34.1-64.8) and 73.3/100 (95% CI: 49.5-100.0) for rural regions (Table 1). The TG estimate from Turkey was not included in this stratification because distinct figures were not provided for rural and urban regions (Aziz *et al.*, 1997). The TG summary is outlined in table 1 and details of individual studies in Appendix 4.

Causes of the treatment gap

Eight studies investigated causes of the TG. Half were conducted in Africa (Elechi, 1991; Preux *et al.*, 2000; Bassili *et al.*, 2002; El Sharkawy *et al.*, 2006) and the other half in Asia (Pal *et al.*, 2000; Asawavichienjinda *et al.*, 2003; Mac *et al.*, 2006; Das *et al.*, 2007). No studies were indentified from Latin America. Two were qualitative, six quantitative and one study combined both methodologies. Most of the studies were small (less than 100 participants), except two that interviewed 229 and 1450 PWE, respectively (Bassili *et al.*, 2002; Das *et al.*, 2007). All the eight studies reported that the cost associated with seeking epilepsy care contributed to the TG (Bassili *et al.*, 2002; Das *et al.*, 2007; Pal *et al.*, 2000; Mac *et al.*, 2006; Preux *et al.*, 2000; Elechi, 1991; Asawavichienjinda *et al.*, 2003; El Sharkawy *et al.*, 2006). Attributed causes of the TG were multiple and overlapping in the two continents, as summarized in table 2. These causes were also similar for rural and urban regions. The highest median (70%) was associated with inadequate skilled manpower and the lowest (18.5%) with long distances to health facilities (Table 2). Non-adherence to AEDs, a factor that also contributes to TG was investigated in two studies (Elechi, 1991; Asawavichienjinda *et al.*, 2003). Details of individual studies are shown in Appendix 5.

Intervention strategies to address causes of the treatment gap

Seven studies were identified that addressed attributed causes of the TG. Five (71%) were conducted in Africa (Adamolekun *et al.*, 1999; Adamolekun *et al.*, 2000; Olley *et al.*, 2001; Berhanu *et al.*, 2002; Feksi *et al.*, 1991) and two (29 %) in Asia (Gourie-Devi *et al.*, 2003; Liu *et al.*, 2003). No studies were indentified from Latin America. Five interventions were solely educational (Olley *et al.*, 2001; Gourie-Devi *et al.*, 2003; Adamolekun *et al.*, 1999; Adamolekun *et al.*, 2000; Liu *et al.*, 2003), one provided AEDs (Feksi *et al.*, 1991) and one combined education with provision of AEDs (Berhanu *et al.*, 2002). The education interventions were modular in nature and were delivered verbally through workshops to PWE and health professionals. They covered different topics such as causes of epilepsy, epidemiology of epilepsy, diagnosis and management of epilepsy, psychosocial aspects and community based care. These interventions led to an increase in knowledge among PWE and health professionals, as measured by the difference between assessment before and after the intervention (Olley *et al.*, 2001; Gourie-Devi *et al.*, 2003; Adamolekun *et al.*, 1999; Liu *et al.*, 2003). In addition, education led to an increase in patient recruitment (Adamolekun *et al.*, 1999; Adamolekun *et al.*, 2000; Berhanu *et al.*, 2002). Though information pamphlets led to improvements in knowledge and a reduced default rate, they did not have any effect on adherence, as measured by self reports and serum AED levels (Adamolekun *et al.*, 1999; Liu *et al.*, 2003). However, verbal education and drug supply led to an increase in adherence (Feksi *et al.*, 1991; Adamolekun *et al.*, 1999; Adamolekun *et al.*, 2000; Liu *et al.*, 2003). Only one study assessed psychosocial factors, which are known to affect quality of life among PWE. This study reported decreased levels of depression and neurotic disorders in the group receiving education (Olley *et al.*, 2001). Details of individual studies are summarized in Appendix 6.

Discussion

Magnitude of the treatment gap

A comprehensive search of the literature identified only twelve studies that estimated the magnitude of the TG: this paucity of studies substantiates Kale's findings that the TG as an outcome measure is not well studied in the developing world (Kale, 2002). The results of this review show that the pooled TG estimate of 56% is lower than the 90% that is widely quoted in many studies (Scott *et al.*, 2001; Dua *et al.*, 2006; Diop *et al.*, 2003; Diop *et al.*, 2005; Shorvon & Farmer, 1988) although the CI are wide. The higher estimate is not based upon systematic review of the data and does not provide confidence intervals. To the best of our knowledge, this is the first study that comprehensively reviews the literature to assess the variability of the TG using a robust and reproducible method. The few narrative reviews that have been conducted in developing countries have addressed the epidemiology of epilepsy with a mention of the TG (Bharucha, 2003; Mac *et al.*, 2007; Sridharan, 2002; Shorvon & Farmer, 1988; Rajbhandari, 2004; Ray *et al.*, 2002).

A substantial amount of variation in the TG among studies was demonstrated by graphical display of the estimates, a statistical test of heterogeneity and a measure of inconsistency. The pooled estimate, using a method that corrects for among study variation, provides a meaningful indication of the magnitude of the TG. When stratified by continent, studies conducted in Africa had the highest variability whereas Latin America had the lowest. Variability was also higher in rural compared to urban areas (Table 1), although none of the studies in this review attempted to identify specific reasons for such rural/urban differences.

Though we did not investigate sources of heterogeneity, some variation in estimates may be explained by a failure to calculate the TG uniformly. Seven studies calculated it using active epilepsy as the denominator (Aziz *et al.*, 1997; Radhakrishnan *et al.*, 2000; Coleman *et al.*, 2002; Wang *et al.*, 2003; Medina *et al.*, 2005; Dent *et al.*, 2005; Noronha *et al.*, 2007) and four used both active and passive epilepsy (Mendizabal & Salguero, 1996; Nicoletti *et al.*, 1999; Ndoye *et al.*, 2005; Somoza *et al.*, 2005). In addition, studies defined active epilepsy differently: Eight confined it to five years, according to the ILAE definition (Coleman *et al.*, 2002; Aziz *et al.*, 1997; Nicoletti *et al.*, 1999; Radhakrishnan *et al.*, 2000; Medina *et al.*, 2005; Somoza *et al.*, 2005; Dent *et al.*, 2005; Mendizabal & Salguero, 1996), two limited it to one year (Ndoye *et al.*, 2005; Wang *et al.*, 2003), whereas one study used two years (Noronha *et al.*, 2007). Other factors that might have contributed to heterogeneity include different study populations, unskilled manpower in rural settings, variable socioeconomic conditions and diverse levels of health care development in the study regions (Nicoletti *et al.*, 1999; Jallon, 1997). The study by Somoza et al, which had the widest CI (Fig 1), consisted of school children and only a small number failed to seek treatment. This could have been influenced by the high level of literacy and the study setting, which was described as a district where social, economic and health indicators ranked among the country's highest and reached levels comparable to developed countries.

Causes of the treatment gap

We found that attributed causes of the large TG in developing countries were multiple and overlapped between continents (Appendix 5). All the eight studies included in the review reported that the cost of seeking epilepsy treatment was associated with the TG in developing countries (Bassili *et al.*, 2002; Das *et al.*, 2007; Pal *et al.*, 2000; Mac *et al.*, 2006; Preux *et al.*, 2000; Elechi, 1991; Asawavichienjinda *et al.*, 2003; El Sharkawy *et al.*, 2006). The attributed causes with the highest medians were related to the health systems mainly: inadequate skilled manpower, cost of treatment and unavailability of drugs. This indicates that health system issues are a major obstacle for TG. Though individual perceptions such as

cultural beliefs, traditional treatment and distance to health facilities had lower medians, they greatly influence treatment seeking among PWE. The findings of this review show that superstations and cultural beliefs influence PWE to seek treatment from traditional healers instead of allopathic practitioners (Pal *et al.*, 2000; Preux *et al.*, 2000; Asawavichienjinda *et al.*, 2003; El Sharkawy *et al.*, 2006; Das *et al.*, 2007). Shorvon *et al* also observed that many patients spent considerable amounts of money to obtain traditional cures and it was common for patients to travel hundreds of miles or donate treasured items to a healer in return for antiepileptic treatment (Shorvon & Farmer, 1988). This negates the usefulness of the advances made in the diagnosis and treatment of epilepsy (Das *et al.*, 2007; Leppik, 1988) hence the need for comprehensive programs to address these attributed causes.

Intervention strategies to address causes of the treatment gap

The results of this review suggest that some attributed causes of the TG in developing countries can be addressed through educational interventions and supply of AEDs. Such interventions should target health providers (including traditional healers), PWE and the wider community (Scott *et al.*, 2001; Berhanu *et al.*, 2002). The interventions should be tailored to the needs of each target group: those for health providers should be geared towards improving skills in diagnosis and management of epilepsy whereas for PWE emphasis should be on adherence, when and how to take AEDs as well as how to live with epilepsy. They should also include psychosocial aspects of epilepsy that may lead to the development of a positive attitude towards PWE which is essential in improving quality of life and treatment (Jallon, 1997). Educational interventions in developed and developing countries have been shown to improve epilepsy knowledge, AED adherence, seizure outcome and self-esteem among PWE (Olley *et al.*, 2001; Gourie-Devi *et al.*, 2003; Adamolekun *et al.*, 1999; Liu *et al.*, 2003; Berhanu *et al.*, 2002; Snead *et al.*, 2004; Helde *et al.*, 2003; Helde *et al.*, 2005; Clark *et al.*, 2001; May & Pfafflin, 2002; Wohlrab *et al.*, 2007; Helgeson *et al.*, 1990). Other studies have suggested that adequate drug supplies have to be provided for the success of any epilepsy management program (Gourie-Devi *et al.*, 2003; Feksi *et al.*, 1991; Mani *et al.*, 2001; Watts, 1989). However, experience in developing countries with other major public health problems, particularly communicable diseases, has demonstrated that simply delivering drugs to these countries will not necessarily reduce the TG (Reynolds, 2000). This indicates that health system interventions are not sufficient on their own. There is need to accompany such interventions with non-pharmacological, community-based interventions in order to reduce the stigma of epilepsy and reduce barriers to effective care (Krishnamoorthy *et al.*, 2003).

Limitations of the review

Studies may not have been identified at the search stage if they were not indexed in the three databases used or not published in mainstream journals. Studies on causes and interventions varied in the population studied, selection procedures, methods of ascertainment, study length and outcomes measured. Due to these variations, data from separate studies could not be statistically combined. Numeric estimates were not available for some quantitative outcomes in intervention studies hence descriptive statistics were not calculated for this section of the review. Studies that investigated the TG were independent of those that instituted interventions; hence it was not possible to compare differences in the TG before and after an intervention. We did not investigate the potential sources of heterogeneity due to the small number of studies and inadequate variables in studies that estimated the TG. Though we included all languages during the search, we were not able to translate two Chinese papers reporting magnitude of the TG, although the abstracts indicated an estimate similar to the included studies.

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Conclusion

This review provides a more accurate pooled estimate of the TG in developing countries with confidence intervals. Furthermore, it provides attributed causes of the gap and lists interventions that have been implemented to improve outcome in developing countries. Given the economic, social, political and cultural context of the TG, there is need for future research to focus on well-planned and coordinated interventions. The findings of this review suggest that such interventions should consider the medical, developmental and psychosocial needs of PWE as well as being financially, geographically and culturally accessible. These interventions should also involve health system personnel as well as other personnel such as traditional healers who incorporate cultural beliefs and provide more comprehensive care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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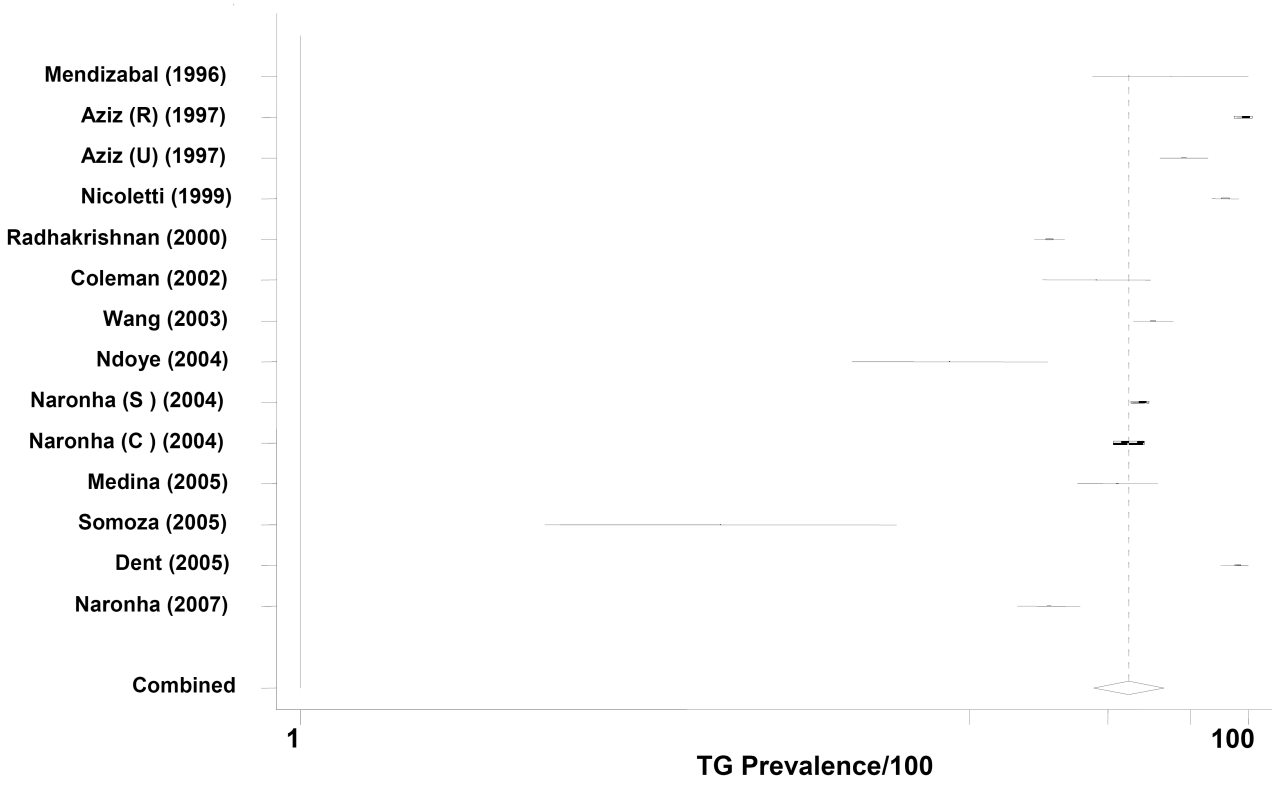

Figure 1.
Forest plot for the epilepsy treatment gap prevalence

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Table 1

Magnitude of the epilepsy treatment gap by region and location

Continent/Location	No of studies	TG%	L 95% CI	U 95% CI
Latin America	7	55.4	39.0	78.6
Asia	4	64.3	24.3	100.0
Africa	3	48.9	14.3	100.0
Urban	7	46.8	34.1	64.2
Rural	7	73.3	49.5	100.0

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Table 2

Cause of the epilepsy treatment gap expressed as median and range

Causes of ETG	No of studies	Median (%)	Minimum (%)	Maximum (%)
Cost of treatment	8	62	11	90
Superstitions and cultural beliefs	5	40	7	65
Unavailability of drugs	5	53	18	44
Long distance to health facilities	3	18.5	18	19
Traditional treatment	3	44	6	82
Inadequate skilled manpower	3	70	64	76