Identification and management of depression in primary care settings. A meta-review of evidence

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SUMMARY. **Aim** – The purpose of this review is to summarize the evidence base on the effectiveness of (a) screening for depression in primary care; (b) managing depression in primary care employing specific management strategies; (c) treating primary care depressive patients with antidepressants. **Methods** – Meta-review of all available reviews of the evidence. **Results** – Screening alone does not improve the recognition, management and outcome of depression in primary care settings. Management strategies, including (a) training primary care staff, (b) consultation-liaison, (c) collaborative care, (d) replacement/referral are supported by insufficient evidence to provide a definite answer as to the clinical effectiveness of individual models. Robust evidence exists to encourage physicians to prescribe effective doses of antidepressants in patients with moderate to severe depression who seek treatment in primary care settings. **Conclusion** – Population-level screening campaigns have a negative ratio of costs to benefits. However, at an individual-level of care increasing the ability of primary care physicians in recognising depression remains a relevant factor. Primary care physicians should consider whether depression is mild, moderate or severe. This patient categorisation help develop appropriate management and therapeutic strategies.

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TERMS OF REFERENCE

Over the past two decades, after the pioneering work of Michael Shepherd (Shepherd *et al.*, 1966; Shepherd, 1995), the growing awareness of the sheer size of psychiatric morbidity not referred to and/or not treated by mental health services, and the need to acknowledge the central role of the primary care physician in the early detection of mental distress, has led to the evolution of primary care psychiatry as a field in its own right (Üstün *et al.*, 1995; Kerwick *et al.*, 1997). Then, epidemiological studies conducted in the primary care sector have shown that about half of patients who met criteria for a psychiatric disorder escape the recognition by physicians and only a minority of them receive an appropriate treatment (Goldberg, 1984; Goldberg *et al.*, 1988; Tansella, 2000). In particular, such findings have been confirmed for depression: a great number of epidemiological and clinical studies consistently showed that 10% to 50% of primary care patients suffering from clinically relevant depressive symptoms are not diagnosed by their physician (Simon & Von Korff, 1995). These figures are in line with physicians' perception that recognising depression is patients who present in a busy primary care setting, often with totally unrelated complaints or with poorly defined or hidden signs or symptoms, is not an easy task for the clinician (Kassianos, 2006). Additionally, the development of effective management strategies, including rational use of antidepressive drugs, is similarly difficult, and still unclear is whether these management strategies have a positive impact on patient outcomes, especially in the long-term (Simon *et al.*, 1995; Tiemens *et al.*, 1996; Simon, 2001).

In recent years physicians, public health administrators and policy makers tend to increasingly base their decisions on available evidence collected by means of randomised controlled trials, and systematically reviewed by means of meta-analytical procedures (Black, 2001). This review will employ a similar methodological framework, and will be organised as a meta-review, that is, a review of all available reviews of the evidence. The evidence base on the effectiveness of the following three

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aspects will be considered: (a) screening for mental distress in primary care, with specific focus on depression; (b) management of mental distress in primary care; (c) antidepressant drug use in primary care.

SCREENING FOR MENTAL DISTRESS IN PRIMARY CARE

Although early studies demonstrated that the improvement of physicians' ability to detect depression and mental distress represented a crucial step in reducing the social impact of these disorders, more recent studies on the usefulness and long-term effect of screening and case findings instruments provided contradictory results (Gilbody *et al.*, 2006). The key question, at this regard, is whether high quality randomised controlled trials, and systematic reviews of these trials, provided evidence that screening for depression in primary care effectively reduces morbidity.

Evidence base

Three systematic reviews have been performed with the aim of clarifying whether screening and case finding instruments improve the recognition of depression. In 1996 the US Preventive Services Task Force (USPSTF) recommended that clinicians "maintain an especially high index of suspicion for depressive symptoms in adolescents and young adults, persons with a family history of depression, those with chronic illness, those who perceive or have experienced a recent loss, and those with sleep disorders, chronic pain, or multiple unexplained somatic complaints" (US Preventive Services Task Force, 1996). However, the task force found insufficient evidence to recommend for or against routine screening for depression with standardised questionnaires. Six years later, in 2002, the USPSTF reported in *Annals of Internal Medicine* the results of a systematic review of randomised trials conducted in primary care settings assessing the effect of screening instruments for depression (Pignone *et al.*, 2002; US Preventive Services Task Force, 2002). The review found 14 randomised trials assessing the effect of routine screening of adult patients for depression in primary care with usual care. Frequently used case-findings instruments included the *Beck Depression Inventory*, the *Centre for Epidemiologic Study Depression Screen*, the *General Health Questionnaire*, the *Medical Outcome Study Depression Screen*, the *Primary Care Evaluation of Mental Disorders*, the *Symptom-Driven Diagnostic system-primary care and the Zung Self-Depression Scale*. The main outcomes in these studies were differences in physicians' rate of detection or recognition of depression. Included interventions differed in terms of intensity. Some trials provided feedback of screening results alone; others provided feedback and general or specific treatment advice to the physician; and some provided feedback and treatment advice and helped practices develop systematic means of improving the quality of treatment and follow-up. Compared with usual care, feedback of depression screening results given to physicians generally increased recognition of depressive illness in adults. Meta-analysis suggested that screening and feedback reduced the risk for persistent depression (relative risk 0.87, 95% confidence intervals 0.79, 0.95). Interestingly, programs that incorporated interventions aimed at improving recognition with interventions for improving treatment and quality of care had stronger effects than programs of feedback alone. As a consequence of these results, the USPSTF recommended "screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow-up".

In the UK a Cochrane systematic review reached somewhat different conclusions (Gilbody *et al.*, 2005). The researchers included randomised trials of the administration of case finding/screening instruments for depression and the feedback of the results of these instruments to clinicians, compared with no feedback. Included studies were conducted in primary care settings or in general hospitals. Studies investigating the effect of screening strategies in addition to different forms of enhanced care (such as case management) were excluded. A total of 12 studies, including 6000 patients, showed that screening/case findings instruments alone had a borderline impact on the overall recognition of depression by clinicians (relative risk 1.38, 95% confidence interval 1.04, 1.83), while screening plus feedback had no impact on the detection of depression. However, three studies that selected patients scoring above a certain threshold suggested that screening and feedback might be effective in selected patient populations. Based on these findings, authors concluded that practice guidelines to adopt routinely administered case finding/screening questionnaires for depression, in isolation, should be resisted. Authors emphasised that the US review conducted on behalf of the USPSTF found positive evidence for programs that included, in addition to screening tools, enhanced care consisting of face to face education of patients, telephone support, management of drugs, psychotherapy, structured follow-up. Additionally, clinicians were offered guidelines, practice based education, and face to face support

from specialists. In other words, in these studies screening was only one element of the package, and positive outcomes cannot be attributed to screening alone.

In addition to this Cochrane review, in the UK the National Institute for Clinical Excellence (NICE) issued evidence-based guidelines supporting a careful, stepped approach to managing depression in primary care. According to NICE guidelines, screening should be undertaken in primary care and general hospital settings for depression in high-risk groups - for example, those with a past history of depression, significant physical illnesses causing disability, or other mental health problems, such as dementia. Screening for depression should include the use of at least two questions concerning mood and interest, such as: "During the last month, have you often been bothered by feeling down, depressed or hopeless?" and "During the last month, have you often been bothered by having little interest or pleasure in doing things?" However, this recommendation is based on "well-conducted clinical studies but not randomised clinical trials" (Goldberg, 2006).

Very recently, a systematic review and meta-analysis of randomised controlled trials investigating the effect of screening and early psychological intervention for depression in schools identified eight studies (five focusing on children and three on adolescents) (Cuijpers *et al.*, in press). In total, 5803 students were screened. The analysis revealed that the number needed to screen was 31 (95% confidence interval 27, 32), which means that 31 students had to be screened in order to generate one successfully treated case of depression. Psychological treatment was found moderately effective in reducing the burden of disease in these students (effect size 0.55, 95% confidence interval 0.35, 0.76). Although these results are promising, in most countries routine screening in students is not recommended. In the US the USPSTF found limited evidence on the accuracy and reliability of screening tests in children and adolescents and limited evidence on the effectiveness of therapy in children and adolescents identified in primary care settings.

MANAGING MENTAL DISTRESS AND DEPRESSION IN PRIMARY CARE

One of the key underlying assumptions of all screening programs is the availability of effective management strategies intended to improve quality of care and patient outcomes (Tylee & Jones, 2005). However, improving quality of mental health care, and patient outcomes, is a very difficult task, and many different management strategies have been developed during the last few decades in different countries (Bower & Gilbody, 2005). According to Bower & Gilbody (2005), management strategies can be categorised into four models: (a) training primary care staff; (b) consultation-liaison; (c) collaborative care; (d) replacement/referral. In these models the role and involvement of primary care physicians differ substantially: it is crucial in the training model and progressively decreases in the consultation-liaison, collaborative care and replacement/referral. Given the existing trend in using research evidence, especially systematic reviews, in the development of health policies, a key question is whether high quality randomised controlled trials, and systematic reviews of these trials, provided evidence that training, consultation-liaison, collaborative care and replacement/referral have a beneficial role in the management of mental distress in primary care.

Evidence base

(a) Training primary care staff

Two systematic reviews evaluated the beneficial effects of training. Gilbody and colleagues analysed 10 randomised trials, 5 controlled before and after studies and 2 interrupted time-series that investigated the effectiveness of guideline implementation and other educational strategies in depression (Gilbody *et al.*, 2003). In these studies complex interventions involved videos, written material, small group teaching sessions and role-play delivered by multi-disciplinary teams. Less complex interventions involved guideline implementation strategies, clinician education, educational meetings. All these guideline and educational strategies resulted largely ineffective in terms of clinical improvement, quality of life and depression outcomes. However, evidence suggests that education increases antidepressant prescribing, but not depression outcomes, in primary care settings. Authors noted that guideline implementation and educational interventions were effective only when embedded in intensive forms of continuous improvement, such as nurse case management, collaborative care or other similarly intensive quality improvement strategies.

The second review included randomised trials of effectiveness of specific psychosocial interventions for depression and somatisation delivered by primary care physicians (Huibers *et al.*, 2003). Two studies showed that problem-solving treatment by a primary care physician is as effective as antidepressant therapy in the treatment of major depression. One additional trial reported that training primary care clinicians in problem solving in depression was more effective than placebo. In two studies that

included patients with somatisation disorder, training primary care physicians in somatisation was more effective than usual care in improving patient outcomes.

(b) Consultation-liaison

The concept of consultation-liaison refers the potential for education and skill sharing from primary to secondary care. Gask and colleagues described four main aspects (Gask *et al.*, 1997): regular face-to-face contact between psychiatrist and primary care physician; psychiatric referral only takes place after discussion at face-to-face meeting; some cases are managed by the primary care physician only (after appropriate discussion); when referral does take place there is feedback to the primary care physician and management by them. Bower and Sibbald, who systematically reviewed the effect of consultation-liaison on the clinical behaviour of primary care, reported their findings in two systematic reviews (Bower & Sibbald, 2000a, b). Twelve studies used consultation-liaison models involving a variety of mental health professionals: psychiatrists, psychologists, community nurses and multidisciplinary community mental health teams. Co-interventions included didactic teaching, case-by-case consultation and team meetings, provision of information, medication adherence surveillance, combined interviews, case conferences, academic detailing, feedback of assessments, and structural changes such as lengthening medical appointments. The analysis showed that consultation-liaison models had a direct effect on primary care physician prescribing behaviour when used as part of complex, multifaceted interventions. According to study authors consultation-liaison interventions caused changes in psychotropic prescribing, but these were short-term and limited to patients under the direct care of the mental health professional. Authors advocated for longer-term studies assessing the degree to which demonstrated effects endure over time. A third review, published in 1994, included two studies which showed no beneficial effect on patient outcomes (Katon & Gonzales, 1994).

(c) Collaborative care

Gilbody and colleagues, who systematically reviewed interventions to improve the quality of care for depression, showed that collaborative care, that is programs involving patient education, shared care among the primary care physician, psychiatrist, or psychologist were associated with beneficial effects in terms of patient recovery in two randomised trials (Gilbody *et al.*, 2003). Collaborative care may additionally be of beneficial effect in patients at high-risk of recurrence and in those with late-life depression. A related form of collaborative care, called stepped collaborative care, offered enhanced care for those not responding to usual care by primary care physician. Stepped collaborative care involved patient education, clinician education meetings, automated pharmacy data, and enhanced collaborative management by a psychiatrist in a primary care setting. After six months of this intervention, medication adherence and recovery was improved, with benefits persisting for up to 28 months for those with moderately severe depression. The efficacy of a complex package of care, involving patient screening by questionnaire, clinician education, opinion leaders, patient-specific reminders, nurse case-management, and integration with specialist care, was assessed by two randomised studies that showed a beneficial effect at 12 months in terms of antidepressant medication adherence and depressive symptoms. However, the benefits for depression outcomes were no longer evident at 24 months. A recently published systematic review included studies specifically investigating the effect of case management to improve major depression in primary care (Gensichen *et al.*, 2006). Thirteen studies met the inclusion criteria, of whom 11 were meta-analysed. Results suggested a positive effect on all outcomes assessed, including symptom improvement, remission, response, and adherence.

Several randomised studies provided evidence that nurse case management improves outcomes for depression. The terms nurse case managements implies complex intervention strategies where nurses received training in the management of depression, and they provided patient education and ongoing support and monitored therapy, outpatient attendance, and treatment response according to well-established algorithms. Overall, collaborative care was associated with positive outcomes in 11/14 randomised trials (Gilbody *et al.*, 2003). Similar results were obtained by Von Korff and colleagues, who reviewed 12 randomised trials of collaborative care in major depression (Von Korff M. & Goldberg, 2001), while Badamgarav and colleagues specifically assessed the effectiveness of disease management programs in depression (Badamgarav *et al.*, 2003). Disease management programs were defined as interventions to manage or prevent a chronic condition by using a systematic approach to care (for example evidence-based practice guidelines) and potentially employing multiple treatment modalities. This systematic review identified 19 studies, of whom 15 were carried out in the US, two in the United Kingdom, one in Australia and one in Canada (Badamgarav *et al.*, 2003). Seventeen studies used a randomised, controlled design. Pooled results for disease management program effects on symptoms of depression

showed statistically significant improvements. Programs also had statistically significant effects on patients' satisfaction with treatment, patients' compliance with the recommended treatment, and adequacy of prescribed treatment. Interestingly, disease management programs increased health care utilization and treatment costs.

(d) Replacement/referrals

Bower and Sibbald categorised interventions for depression as "replacement" or "consultation-liaison" models, where replacement was the provision of care by mental health professionals, while consultation-liaison intended to change the behaviour of primary care physicians (Bower & Sibbald, 2000b). According to Bower and Sibbald systematic review, twenty six studies used replacement models involving counsellors, psychologists, community nurses or nurse therapists, psychiatrists and social workers (one study) (Bower & Sibbald, 2000b). Treatments provided by these mental health professionals included non-directive counselling, behaviour therapy, cognitive-behaviour therapy, cognitive analytic therapy, brief dynamic psychotherapy, problem solving therapy, practice-based psychiatric clinics, medication adherence counselling and social casework. Authors found some evidence that replacement models achieved significant short-term reductions in primary care physician psychotropic prescribing and mental health referral, but the effects were not reliable and not maintained in the long-term. Other systematic reviews provided similar findings, with moderate to medium effect sizes more often reported (Balestrieri *et al.*, 1988; Brown & Schulberg, 1995; Churchill *et al.*, 1999; Bower & Sibbald, 2000c; Schulberg *et al.*, 2002).

ANTIDEPRESSANT DRUG USE IN PRIMARY CARE

In the field of depression, effective management strategies intended to improve quality of care and patient outcomes include the use of pharmacological treatments of proven effectiveness (Spigset & Martensson, 1999). Since the introduction in the late 1980s of the selective serotonin re-uptake inhibitors (SSRIs) and newer antidepressants (ADs), in most countries the number of AD prescriptions has progressively increased (Middleton *et al.*, 2001; Ciuna *et al.*, 2004; Poluzzi *et al.*, 2004; Helgason *et al.*, 2004; Hunkeler *et al.*, 2005). AD agents are indicated in the pharmacological treatment of major depression but, in recent years, new labels have been increasing the number of psychiatric disorders where these agents are indicated, and new patient populations, such as the elderly, children and adolescents, have been suggested as possible target of AD therapy. Although a relevant proportion of these prescriptions are issued by primary care physicians, only a minority of randomised controlled trials investigating the effectiveness of antidepressants in depressed patients were carried out in the general practice, and these trials typically enrolled patients with major depression of at least moderate severity (Barbui & Garattini, 2006). From a clinical viewpoint it is therefore crucial to ascertain whether high quality randomised controlled trials, and systematic reviews of these trials, provided evidence that antidepressants should be routinely prescribed to individuals with depressive symptoms seeking help in primary care settings.

Evidence base

A recently performed systematic review of trials investigating whether antidepressants are effective in general practice patients with major depression identified only ten studies comparing tricyclic antidepressants (TCA) with placebo, three comparing selective-serotonin reuptake inhibitors (SSRIs) with placebo, and two comparing both drug treatments with placebo (Arroll *et al.*, 2005). Studies were short-term, only 535 patients received treatment with TCA and 552 with SSRIs (in the efficacy analysis), and outcome measures typically included rating scales with items concerning sleep and anxiety, which could have influenced the comparisons. In addition to these limitations, in most such studies scores on rating scales were dichotomised, and results were presented in terms of proportion of responders. Although from a practical viewpoint this seems very reasonable because it allows physicians to make a reasoning in terms of proportion of patients (and not in terms of means and standard deviations), it has been noted that this approach systematically magnifies the effect of new medicines against placebo (Moncrieff & Kirsch, 2005). Additionally, in terms of continuous outcome measures, only a modest effect for TCAs (for depression scores the standardized mean difference versus placebo was - 0.42 [95% confidence interval -0.55 to -0.3]) was observed, while no data could be summarized for SSRIs on a continuous outcome. In general, a standardized mean difference of at least 0.5 is required for a claim of medium effect size. Even assuming that most patients included in this analysis were suffering from mild depression, a balanced interpretation of these results suggests that the efficacy of antidepressants in the treatment of general practice patients with mild depression is sparse and inconclusive.

Regarding the compelling issue of whether new generation antidepressants or old generation antidepressants should be routinely prescribed, MacGillivray and colleagues, who carried out a systematic review of trials comparing SSRIs with TCAs in the general practice, showed that, although only 11 studies of variable quality were identified, no differences could be detected, in terms of efficacy and in the short term, between the most commonly prescribed classes of antidepressants (MacGillivray *et al.*, 2003). However, there are data suggesting that old antidepressants have the edge over SSRIs in terms of efficacy, as shown by systematic reviews of trials conducted in patients with major depression recruited in specialised settings (Anderson, 1998; 2000; 2001; Barbui & Hotopf, 2001).

IMPLICATIONS FOR PRACTICE

The evidence that screening alone does not improve the recognition, management and outcome of depression in primary care settings implies that population-level screening campaigns have a negative ratio of costs to benefits. However, increasing the ability of primary care physicians in recognising depression in primary care patients remains a relevant factor at an individual-level of care. Primary care physicians should reflect on their ability in interviewing patients, considering that the lack of psycho-social cues from patients and of patient-centred skills contributed to the non recognition of emotional distressed patients (Del Piccolo, 2000). Moreover, active facilitation of the presentation of psychosocial topics improves the recognition of emotional distress (Zimmermann *et al.*, 2003). During everyday clinical practice, primary care physicians need to take into careful consideration any previous history of depression, unexplained physical symptoms, physical illness and disability, other medical conditions such as Cushing's syndrome, therapeutic use of corticosteroids, pregnancy or recent delivery, premenstrual syndrome or menopause, as well as recent significant life events, including birth, death, marriage, divorce, moving house, collapse of a business, redundancy, inability to find a job (Del Piccolo et al., 2002; 2004). Any recent changes in patient moods, such as feeling down, depressed or hopeless, should be recognised, highlighting typical diurnal variation in symptoms (patients usually report to feel a bit better in the evening than in the morning). Depressed patients lack energy, motivation and appetite, as well as interest in work and social life. Depressive symptoms are often associated with anxiety, eating disorders, obsessive-compulsive disorder, panic disorder, chronic fatigue syndrome and other psychiatric comorbidities. Primary care physicians should inquire about drug and alcohol use and abuse. Disorders of the content of thought (delusions and hallucinations) are uncommon but should be similarly investigated, given that occur in a minority of cases (psychotic depression). Patients should be asked about feeling of worthlessness and guilt, as well as about thoughts of suicide.

At this stage, primary care physicians should consider whether depression is mild, moderate or severe. Mild to moderate depression is characterised by depressive symptoms and some functional impairment; severe depression is characterised by depressive symptoms, functional impairment, agitation or psychomotor retardation, and marked somatic complaints. This patient categorisation help develop appropriate management and therapeutic strategies. For example, the available robust evidence of efficacy of antidepressant treatment in secondary care settings, where patients with moderate to severe depression are usually treated, should encourage physicians to prescribe effective doses of these drugs in patients with moderate to severe depression who seek treatment in primary care settings (Cipriani *et al.*, 2005). Conversely, the lack of strong evidence of efficacy of antidepressant treatment in primary care settings, where patients with mild depression are usually treated, should encourage physicians not to prescribe antidepressants in patients with mild depression who seek treatment in primary care settings.

Unfortunately, in real-life primary care settings, although some qualitative studies exploring how primary care physicians decide to prescribe antidepressants suggested that the preferred strategy, theoretically, is to "wait and see", the dramatic increase in antidepressant sales and consumption indicates that prescriptions have progressively become automatic answers to patients' psychological distress (Barbui & Tansella, 2005). This may explain why drug companies continue to give economic support to training courses based on lectures and passive listening, even though these educational programmes are not convincingly effective in improving recognition and outcome; clearly, they are convincingly effective in increasing drug prescriptions. This automatism has negative consequences. First, it induces a passive attitude among primary care physicians, who tend to consider antidepressants as their only therapeutic strategy, therefore not taking into consideration the possibility of developing more specific and individualized treatment plans, including, for example, watchful waiting or psychological/psychosocial interventions backed by scientific evidence. Second, a passive attitude is inevitably induced in patients, who receive a message suggesting that modifi-

cations of thought, mood and conduct can be achieved by pharmacological means only.

Third, there is a crucial problem of *coverage and focusing of antidepressants* in the general population (Tansella, 2006; Paykel, 2006; Goldberg, 2006; Weissman, 2006). In a study conducted among Italian primary care physicians the *coverage of antidepressants* (the proportion of those receiving antidepressant prescriptions of all those who might be expected to benefit from them) was 39.3% only (Bellantuono *et al.*, 2002). From this and other studies it is clear that we need to increase dramatically, in several settings, but especially in the primary care, the proportion of depressed people who receive attention and treatment. It appears also that there is much capacity for improving the *coverage* of antidepressant drug prescription. All drug companies producing antidepressants are very keen to increase the *coverage* of these drugs (especially of the newer, more expensive products), making it as close to 100% as possible. However, we are missing reliable estimates of focusing, i.e. the proportion of those receiving antidepressants who needed them. How far from the ideal 100% is focusing now, under the present circumstances (with a coverage of less than 40%)? To what extent may focusing further decrease, under the pressure of prescribing more antidepressants in the attempt to enhance their coverage and to fill the gap between rates of depression and depression actually treated? We cannot continue to draw attention to the undiagnosed and under-treated depression without considering at the same time the inappropriate practice in the use of antidepressants and the possibility that this inappropriate use may further increase as the result of campaigns to prescribe more antidepressants for filling the above mentioned gap. We need to improve the recognition of "true", clinically significant depression that may benefit from drug treatment, as well of mild depression and to improve the quality of all treatments (not only pharmacological), and the extension and quality of social support made available to people suffering from mild or severe depression.

Evidence- and public health-based action is therefore required. At the individual level primary care physicians should consider that the efficacy/safety profile of antidepressants has been demonstrated in adults with moderate to severe depression only, and that extrapolating these data to other patient populations, such as individuals with mild depressive symptoms, or adolescents with psychological problems, might be inappropriate. Psychotherapies should more often be considered as treatment of milder depression or as an adjunct to antidepressant drugs in more severe illness. At the epidemiological level, we need more data collected under real word circumstances to establish the effect of these prescribing practices on the course and outcome of depression in the general practice, in order to ascertain the degree of coherence between beneficial and adverse outcomes measured in experimental conditions and outcomes measured in real-word settings.

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