

Challenges in remaining "UpToDate": A case study identifying errors in evidence-based point-of-care resources

Vinita Akula^{1*}, Kevin Dick²

¹Florida State University College of Medicine, Tallahassee, FL, United States of America

²Systems & Computer Engineering, Carleton University, Ottawa, ON, Canada

*Author for correspondence (va18b@med.fsu.edu)

Abstract:

Our understanding of the prevalence of mental health disorders (MHDs) in society is in the midst of a paradigm shift: where MHDs were once considered rare within a population, studies through the last decade have converged to the conclusion that they are, in fact, near universal. Consequently, the demand for mental health treatment has resulted in the training of Primary-Care Physicians (PCPs) to identify, diagnose, and treat common MHDs. As generalists, PCPs require specialised point-of-care clinical resources to educate their patients and provide them with evidence-based treatment plans; UpToDate is one such resource. As a database of synthesized peer-reviewed medical information, written and approved by physician-experts from their review of contemporary peer-reviewed literature, this resource is considered a gold standard. Here, we examine an MHD-specific investigative case study on Generalized Anxiety Disorder where the synthesized UpToDate medical information was found to be in conflict with the original studies. In this era of unrelenting bombardment of digital data, the responsibility of assessing the truth of the information falls to the consumer. While a reliance on reputable information-sharing platforms facilitates both the access and assessment of truth, we discuss the risks of unintended errors, their propagation, and the potential impact at the point-of-care.

Introduction

Individuals who experience mental health disorders (MHDs) have been assumed to be relatively rare within a population. Conversely, individuals who live MHD-free lives are considered prevalent, commonplace, and consequently, are overlooked. Given that the majority of MHD prevalence evaluations are based on point-based, cross-sectional analyses of a population, where the number of MHD cases currently observed in the population are examined *at a single point in time*, these assumptions hold true [1]. However, a *longitudinal* view of lifetime prevalence reveals these disorders to be much more commonplace than originally assumed, resulting in a paradigm shift in our view of MDH in society [1]. Through the past decade, population-representative estimates have converged to the conclusion that diagnosable disturbances in behavioural or emotional health at some point in an individual's life is near universal [1] and, most worryingly, the rate of mood disorders and suicide-related outcomes have increased significantly in specific sub-populations [2].

To illustrate the impact of historical studies on our understanding of the prevalence of MHD in society, consider the simulated and simplified example in Figure 1. The

lifespans of ten individuals are depicted with portions of their relative lifespans highlighted to represent a period in time when they were diagnosed with an MHD. While each individual exhibits a varying number and duration of MHD period within their intra-person lifespans, we highlight that the four cross-sectional studies used to evaluate the point-based prevalence of MHD in this population consistently identifies ~10-20% of the population as having a MHD at each time point (study #1: individuals 2, 7; study #2: individuals 2, 3; study #3: individuals 1, 9; and study #4: individuals 5, 9). Interestingly, this holistic view of MHD periods over individual lifetimes reveals that almost all individuals experience at least one MHD within their lifetimes; only individuals 6 and 10 appear to have lived MHD-free lives. Not explicitly captured in this example is the prevalence of undiagnosed MHD or contextual life-events, factors contributing to additional layers of complexity in appreciating societal impact. Modifying the metric with which we quantify the prevalence of MHD within a population has sweeping consequence across the continuum of care.

With the more holistic understanding of the prevalence of MHD in society comes the realization of the dire

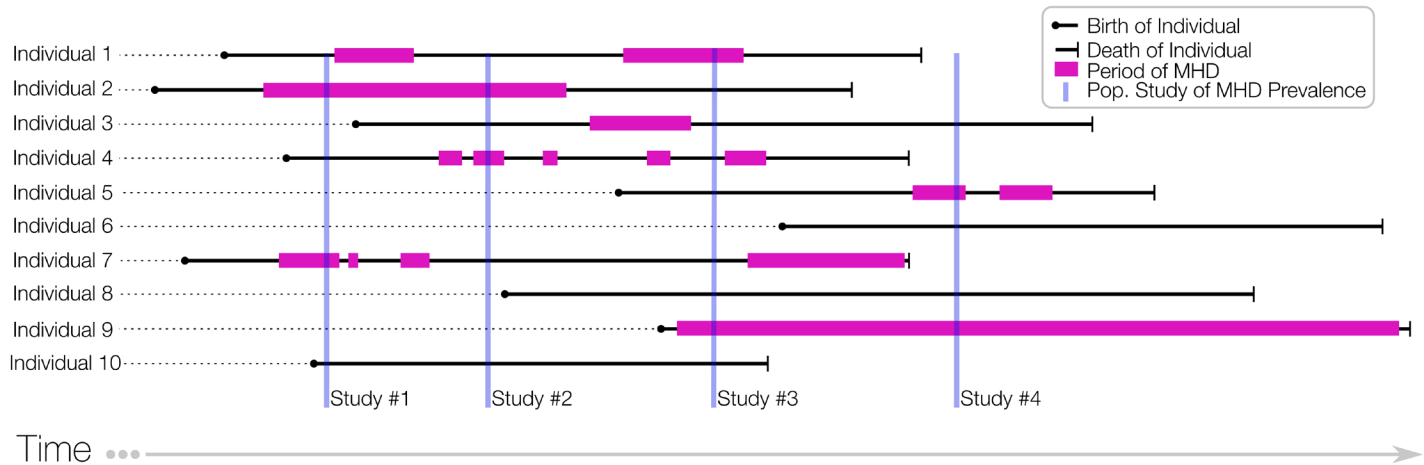


Figure 1 | Simulated example of a series of point-based, cross-sectional studies to determine MHD prevalence. Studies that measure the prevalence of MHDs in a population as the *percentage of the population that are diagnosed with an MHD during the study period* will fail to capture the incidence of MHDs at other periods of an individual's life, that is, the period of time before the study and the period of time following the study. While this figure is a simulated example, by modifying our definition and view of MHD over the course of an individual's lifetime, we can appreciate that MHDs are much more commonplace than originally defined necessitating increased medical support.

need for increased medical support. Unfortunately, the availability of physicians treating MHDs has remained essentially unchanged and has even seen a periodic decline in the number of psychiatrists [3,4], exacerbating the mismatch between MHD treatment supply and demand. With the recognition of this disparity, there has been a concerted effort to train Primary Care Physicians (PCPs) in identifying, diagnosing, and treating common mental health conditions including Depression, Anxiety, and Attention Deficit Hyper-Activity Disorder (ADHD) [5]. Moreover, the vast majority of patients with psychological problems, between 90–95%, are seen only by their PCP [6]. As generalists, PCPs must be trained and provided with clinical resources enabling them to educate patients on their options as part of an evidence-based treatment plan. Evidently, such resources must consolidate the myriad of peer-reviewed research to represent the state-of-the-art in medical treatment. One such resource for evidence-based medicine is the UpToDate electronic resource for clinicians. Unfortunately, despite the best efforts of the curators of such information, these resources are not void of errors. Here, we explore a case study where a PCP leveraging the UpToDate resources may be faced with conflicting information in an effort to educate a patient on their MHD treatment options.

The UpToDate clinical resource for point-of-Care medicine

UpToDate is a subscription-based resource enabling physicians to access current clinical information [7]. Considered to be a gold standard resource for evidence-based medicine, UpToDate's website reports that it is used by over 1.9 million clinicians and over 7,100 physician authors, editors, and reviewers contribute to the synthesis of contemporary medical

research to produce evidence-based recommendations [8]. Articles in the UpToDate system are written by physician-experts who perform a review of literature on specific medical topics and synthesize the salient information. Each article is then peer-reviewed and approved by other physician-experts. In essence, originally peer-reviewed research articles are consolidated within a document that itself undergoes another round of peer-review.

In this information era, UpToDate is one of several clinician-focused tools to facilitate access to evidence-based information at the point-of-care. Two other commonly used resources, DynaMed and Essential Evidence Plus (EEP), publish clinically-organized topics that are readily reviewed and updated. Topics in all three systems include comprehensive reviews of diseases, health conditions, and abnormalities, as well as more targeted topics related to patient evaluation, differential diagnosis, and healthcare management [9,10].

Case study on mental health treatment

Let's consider a hypothetical adult patient who has recently been diagnosed with generalized anxiety disorder (GAD) who expresses concerns about going on medication due to its side effects. Their PCP might wish to consider alternatives to medication such as cognitive behavioral therapy (CBT) and uses UpToDate and related resources to investigate the effectiveness of CBT compared to the first line medication treatment for GAD in adults.

At the time of writing, the PCPs search of "generalized anxiety disorder" in UpToDate returns the top-ranked article entitled "Approach to treating generalized anxiety disorder in adults" that compares and discusses the use of CBT versus medication in newly diagnosed patients with GAD. In

the subsection “Choosing between CBT and medication”, the article cites a meta-analysis including 65 studies that compared CBT to pharmacotherapy and concluded that the effect sizes between the two groups is roughly equal [11]. However, upon further investigation, the study’s conclusions about the differences in efficacy between therapy approaches is weak justification due to the limitations of the meta-analytic methods used. Given the fixed-effect approach the author used in portions of their analysis, the data could not be generalized to the greater population [11].

The UpToDate article cited another meta-analysis which included 79 randomized clinical trials with a total of 11,002 study participants diagnosed with GAD [12]. UpToDate states that the studies evaluating the efficacy of pharmacotherapy and evidence-based psychotherapy found no significant difference in effect sizes between the two groups ($g = 0.59$ vs. 0.76 , respectively). However, further examination of the meta-analysis text itself revealed psychotherapy showed a medium to large effect size ($g = 0.76$), while medication showed a small effect size ($g = 0.38$) on GAD outcomes. UpToDate mis-reported the meta-analysis’ results and erroneously reported the pharmacotherapy effect size for *depression* ($g = 0.59$) rather than GAD ($g = 0.38$). This incorrect citation of the source’s results invalidated UpToDate’s conclusions on the equivalency of CBT and pharmacotherapy. The meta-analysis further describes a secondary analysis that revealed psychotherapies, particularly CBT, had better outcomes among younger patients. In summary, while UpToDate concludes that the treatments are expected to have equivalent effect sizes, the originally cited literature evidences the conclusion that CBT may, in fact, be the superior approach to managing GAD.

Our findings were corroborated by a similar investigation using the EEP and DynaMed resources. Both EEP and DynaMed are evidence-based point-of-care resources designed to assist clinicians. EEP comprises several searchable databases that organize information as topics and sub-topics [10]. Each sub-topic offers a summative “Overall Bottom Line” of the most recent clinical evidence [10]. Similarly, DynaMed organizes information as “Evidence Reports” and assigns a numeric label from 1–3 representing “likely reliable evidence”, “mid-level evidence”, and “lacking direct evidence”, respectively [9]. Additionally, recommendations are assigned a letter from A–C representing “consistent high-quality evidence”, “inconsistent or limited evidence”, and “lacking direct evidence”, respectively [9].

In its “Bottom Line” recommendation, EEP concluded that CBT focusing on overvaluation of worry, worry-proneness, and dealing with uncertainty appeared to be as effective as pharmacotherapy for treating GAD while appearing to have lower attrition and greater durability in adults, children and adolescents [13]. Citing a systematic review of 22 studies with 1,060 participants, 13 studies compared CBT to “treatment as usual” which included pharmacotherapy among other psychotherapeutic methods [13]. The authors concluded that CBT was more effective than “treatment as usual” in

achieving clinical response, as well as reducing anxiety, worry and depression symptoms [13]. The EEP article assigned a strength of recommendation value of B defined as “inconsistent or limited-quality patient-oriented information” [10]. DynaMed cited the same systematic review as EEP, assigning a “Level 2/Mid-Level” evidence grade to the study conclusion that CBT reduces anxiety symptoms in adults with GAD. Level 2 grades are given to outcomes supported by “some method of scientific investigation, but not meeting the quality criteria to achieve Level 1 evidence labeling” [9]. DynaMed did not directly compare pharmacotherapy and psychotherapy in its conclusions; rather, it considered them separately.

Discussion

Whether the prevalence of MHD within a population is perceived as common or uncommon, a patient’s access to the requisite treatment is influenced by a myriad of factors. From the individual’s perspective, physical barriers, perceived trust in healthcare institutions, MHD stigma, financial barriers, and personal motivations are a handful of examples of patient-specific factors limiting access (depicted as bottom-up factors in Figure 2). Conversely, a cascade of top-down, health

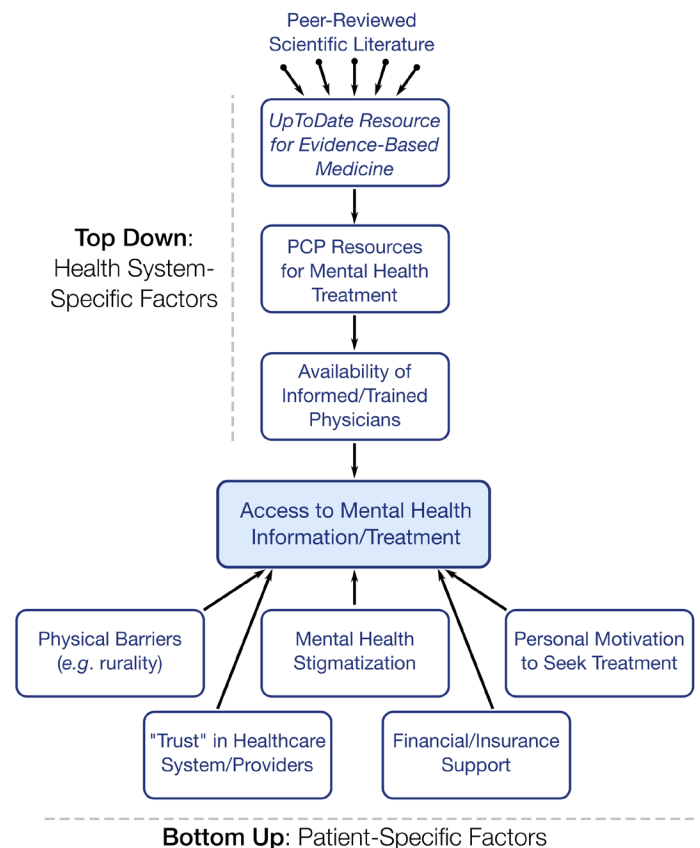


Figure 2 | Flowchart of factors influencing patient access to MHD information and treatment. Top-down factors are a cascade of health system-related factors. Bottom-up factors are independent and patient-specific.

system-specific factors, each dependent on the previous, also limits the supply of MHD-specific treatment (Figure 2). Notably, the availability of the UpToDate resource occurs early in the cascade as it is foundational for developing PCP-specific resources to grow the pool of MHD-knowledgeable physicians. More importantly, a recent study demonstrated that the use of UpToDate reduces diagnostic errors rates [14]. However, a subset of those erroneous diagnoses or management, despite the use of this clinical knowledge support system, may be attributed to potential errors within that system itself.

This case study, specifically, highlights errors within an MHD-related UpToDate article. All too often, peer-reviewed information is taken at face value with the assumption that the scientific publication process strictly enforces truth within the work [15]. Moreover, peer-reviewed articles that synthesize information from other peer-reviewed work (*e.g.* review articles, meta-reviews, textbooks) benefit from a compounding effect; the assumption of their technical correctness is greater still. In Figure 3, we adapted the work of [16] to situate the UpToDate articles within the hierarchy of previously peer-reviewed and published works. As a ‘Summary’, these articles report information that may have gone through upwards of three previous rounds of peer-review [16]. The introduction of any form of error at this level can have widespread and possibly detrimental impact. While the typographic error identified in this case study may appear innocuous at the outset, it did fundamentally reverse the recommended treatment which is an error that may propagate further within the literature or within a patient population. Furthermore, the risk associated to these (allegedly) unintended errors must also be appraised with the risk of intended error or personal biases of the UpToDate authors and editors. A notable medical ethics study investigated the conflicts of interests between UpToDate authors or editors who had a financial relationship with a company whose drug was mentioned in the article; of the medical conditions considered, all UpToDate articles demonstrated a conflict of interest in contrast to DynaMed for which no author or editor had a documented conflict [17]. Finally, UpToDate is often considered an evidence-based resource, however the information reported in the database is not strictly evidence-based. Unfortunately, UpToDate does not share its literature monitoring and search methods which prevents stakeholders from determining whether or not important studies have been overlooked [17]. The UpToDate authors synthesize selected literature with their own domain-specific knowledge to develop patient care recommendations. Ultimately, the interpretation and assessment of this information falls to the consumer, however this poses evident challenges when this information is consumed as part of training material for a non-domain-expert.

With a growing demand for MHD healthcare services, PCPs must be adequately trained and provided the necessary resources to educate and support this patient population. It is an unfortunate reality that scientific research as a whole is in the throes of a “reproducibility crisis” which calls into question the validity of a given research article and

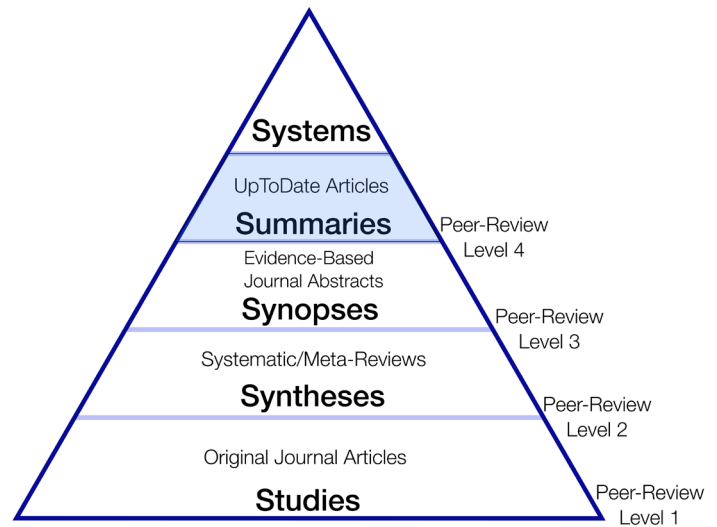


Figure 3 | Adaptation of Haynes' 2006 hierarchy of the "5S" levels of organization of evidence from healthcare research.

erodes the trust in the peer-review process as a whole. In this work, we sought to shed light on the impact of errors within summarized medical recommendations. Finally, this work seeks to open a dialogue on some of the more philosophical foundations at the core of the scientific process: to what extent can we trust *any* peer-reviewed document? How much peer-review is *enough* peer-review? Who is responsible for errors introduced within medical recommendations?

Conclusions

While MHDs were originally understood to be rare within a population, through the last decade, studies have revealed them to be near universal when viewed across an individual's lifetime, commensurately increasing the need and demand for treating physicians. Levied upon the generalists, PCPs require specialised point-of-care clinical resources to educate both themselves and their patients in order to provide evidence-based treatment plans. While the UpToDate database of synthesized peer-reviewed medical information is considered a gold standard, we investigated an MHD-specific case study on GAD and found the synthesized UpToDate medical information to be in conflict with the originally cited studies. This finding, corroborated by other concerns for the independence of recommended treatments in the face of commercial conflicts of interests, inspire discussion about the oversight of documents used in first-line patient treatment. This work is limited to a single case study of a specific illness and a handful of supporting documents, motivating the need for a systematic and independent review of UpToDate to determine the prevalence of errors on the platform. More generally, it is our hope that this work will promote reflection on the validity of multi-peer-reviewed documents, the need for methodologic transparency when synthesizing existing research, and the systematic review of these summaries.

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