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Anticholinergic Burden Measurement in Clinical Pharmacy: Scale Variability, Predictive Validity, and Clinical Utility

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ABSTRACT

Anticholinergic burden scores are used in medication review to make cumulative exposure visible, yet the result depends heavily on the scale selected. This critical integrative review examines contemporary evidence on scale variability, predictive validity, and clinical utility in clinical pharmacy. Drug coverage, potency assignment, dose handling, and local formulary adaptation vary substantially across instruments, so the same regimen can move between burden categories without any change in treatment. Higher scores are repeatedly associated with adverse outcomes, although discrimination and calibration are usually more modest than the association literature suggests and depend on the endpoint being studied. Evidence that score-guided deprescribing improves patient outcomes remains limited. Burden measures are therefore most defensible as case-finding or prioritisation tools that direct attention to potentially important exposure. Medication change still requires pharmacological assessment of the contributing drug, its indication, the plausibility of an adverse effect, and the consequences of changing treatment. Cross-scale agreement, predictive validity, and decision-support utility should be reported separately because evidence for one does not establish the others.

INTRODUCTION

Anticholinergic burden scores can be calculated quickly from a medication list, but their interpretation is partly determined by the instrument used. The same regimen may produce a low or moderate value on one scale and cross a commonly used high-burden threshold on another. That difference is not necessarily a calculation error. Drug inclusion, potency weighting, dose handling, and the age of the underlying formulary vary across scales, so the apparent precision of a single score can conceal a substantial measurement choice.

Cumulative anticholinergic exposure remains a legitimate clinical concern. Medicines prescribed for bladder symptoms, respiratory disease, depression, nausea, allergy, pain, and several other conditions may contribute antimuscarinic effects, while polypharmacy increases the chance that modest contributions accumulate. Population studies continue to show substantial exposure, particularly among older people and patients with complex regimens (Grossi et al., 2020; Reinold et al., 2021). Associations with cognitive decline, falls, mortality, delirium, and medication-related hospital use have made burden scores attractive in pharmacy practice. Much of that evidence, however, comes from geriatric or polypharmacy cohorts in which baseline vulnerability is already high and competing causes of the same outcomes are common. A patient with cognitive impairment, frailty, previous falls, or several sedating medicines may have a high burden score and a high background risk for reasons that are difficult to separate statistically. The signal is clinically useful only if the score has a sufficiently clear meaning for the population and outcome in which it is being used.

Recent reviews have not found convergence on a single reference method. Lisibach et al. (2021) documented wide variation in drug lists and validation approaches, Srikartika et al. (2025) found further differences in the feasibility of applying available measures to administrative data, and Vennard et al.

(2026) concluded that contemporary scales still differ materially in drug coverage and scoring assumptions. No accepted gold standard has displaced that plurality. A patient's measured burden can therefore change because the scale changes, even when the medication regimen does not.

Part of this variation is intentional. The Anticholinergic Cognitive Burden scale was designed around cognitive effects, whereas country-specific instruments attempt to reflect medicines actually used in local practice. The Drug Burden Index is broader still: it incorporates dose and includes sedative as well as anticholinergic exposure, so it should not be treated as an anticholinergic-specific measure that happens to use a different formula. Newer tools such as CRIDECO and the Swedish Anticholinergic Burden Scale were developed because older international lists did not represent every relevant medicine in their settings (Ramos et al., 2022; Rube et al., 2023). If two scales were constructed for different purposes, perfect agreement is not necessarily desirable. The problem appears when both are used to trigger the same clinical action or when their thresholds are treated as equivalent.

A burden score enters clinical pharmacy at the point where a measurement may influence treatment. High values can trigger medication review, electronic alerts, prioritisation, or discussion of deprescribing. None of those actions follows automatically from the number itself. A medicine may remain strongly indicated, an apparent anticholinergic effect may be clinically unimportant, or withdrawal may create a greater problem than continued exposure. Hilmer and Gnjidic (2022) emphasised the gap between burden measurement and the pharmacological judgement required in practice. Intervention evidence is also thinner than the observational literature: trials that reduce anticholinergic medicines have not yet shown consistent improvement in downstream patient outcomes (Braithwaite et al., 2023).

Comparing anticholinergic burden tools therefore requires more than ranking scales by how often they are associated with harm. Cross-scale agreement concerns whether instruments classify exposure similarly. Predictive validity asks whether a score helps distinguish patients who will experience a specified outcome, preferably beyond information already available to the clinician. Clinical utility goes further and asks whether knowing the score changes a medication decision in a way that plausibly improves care. These questions are connected, but the evidence needed to answer them is not interchangeable. A scale can agree closely with another instrument and still predict poorly, while a score associated with harm may never have been tested as a basis for deprescribing. This review examines evidence published from 2020 to 2026 across those distinctions, with particular attention to what a clinical pharmacist can legitimately infer from a burden value and where the current literature remains too indirect for treatment decisions.

RESEARCH METHODS

A critical integrative review with narrative synthesis was used to examine the reliability, variability, and clinical utility of anticholinergic burden measures. This approach was selected because the literature includes heterogeneous designs addressing scale construction, agreement between instruments, associations with clinical outcomes, predictive performance, and the use of burden scores in medication review or deprescribing. Literature searches were conducted in PubMed/MEDLINE and supplemented by backward and forward citation tracking. Eligible studies were peer-reviewed publications from 2020 to 2026 that evaluated the development or comparison of anticholinergic burden measures, their relationship with clinical outcomes, or their application in clinical pharmacy and deprescribing. Studies reporting prevalence alone without contributing to measurement performance or clinical decision-making were excluded.

Evidence was synthesised according to the type of claim supported by each study. Scale-comparison studies were examined for differences in drug inclusion, scoring methods, dose consideration, and agreement between instruments, while prognostic studies were assessed for their ability to relate burden measures to relevant clinical outcomes. Intervention studies were interpreted separately because reductions in anticholinergic burden do not necessarily demonstrate improvement in patient outcomes. Methodological appraisal was qualitative and design-specific, considering population relevance, confounding, validation, outcome directness, and the strength of inference permitted by the study design. Findings were then compared to identify whether variation across studies could be explained by differences in scale construction, population, data source, or clinical endpoint.

RESULTS AND DISCUSSION

1. Sources and Consequences of Cross-Scale Measurement Heterogeneity

Drug coverage remains the first source of cross-scale variation. Lisibach et al. (2021) found substantial differences in the number of medicines included and in the evidence used to assign anticholinergic properties. Vennard et al. (2026) later showed that high-potency medicines still receive inconsistent classifications across contemporary scales, while Srikartika et al. (2025) identified further differences in whether dose, duration, and routinely available prescribing data could be incorporated. Díaz-Acedo et al. (2025) found similar heterogeneity in scales used with chronically treated patients. These are not small cosmetic differences. A medicine omitted from one list contributes nothing to the total regardless of dose or patient response, while the same medicine can materially change the result on another scale. The final sum may be simple, but the rules that determine what enters that sum are not standardised.

Potency values can be based on expert consensus, receptor activity, reported adverse effects, previous scales, or combinations of these sources. Nishtala et al. (2024) examined drugs classified by the Anticholinergic Cognitive Burden system and showed why an ordinal category does not map neatly onto every pharmacological property relevant to clinical effects. Central exposure is also influenced by factors that a list-based score rarely represents well. Two drugs carrying the same nominal burden may differ in central nervous system penetration, dose-response behaviour, or the likelihood that a reported symptom is actually produced by the medicine.

That limitation becomes visible when clinical adverse-reaction data are compared with the lists themselves. Pecquet et al. (2026), using the French pharmacovigilance database, found anticholinergic adverse reactions involving medicines that were omitted from some of 22 scales or assigned relatively low values. Spontaneous reports cannot provide incidence and do not establish the correct score for a drug, but they show that a fixed list can fail to represent medicines encountered in practice. Local prescribing adds another source of divergence. Hwang et al. (2021) validated a Korean scale against emergency visits for anticholinergic adverse events, while Rube et al. (2023) developed the Swedish Anticholinergic Burden Scale because existing tools did not adequately cover medicines used in Sweden. When Swe-ABS was later compared with ACB in a memory clinic, substantially more patients were classified as exposed or high burden (Rube et al., 2026). The difference may reflect better local drug coverage, greater sensitivity, or a broader definition of relevant exposure. Cross-scale comparison alone cannot determine which of those explanations is correct, and the higher classification rate should not be equated automatically with better clinical validity.

Updated drug coverage can improve local relevance without proving that a new instrument is biologically more accurate. Ramos et al. (2022) encountered this problem when developing CRIDECO in Spain. Adding or reclassifying medicines altered the burden assigned to patients with memory complaints, but agreement with an older scale could not serve as a definitive reference because the older scale was itself one of the objects under evaluation. Direct concordance data make the practical consequence clearer. Tristancho-Pérez, Villalba-Moreno, Santos-Rubio, et al. (2022) compared ten scales in at-risk populations and found agreement ranging from poor to substantial. Some pairings behaved reasonably alike; others placed patients in markedly different categories. When burden thresholds are used to trigger review, the disagreement is no longer merely methodological. A patient can receive additional pharmacy attention, or none, because the instrument changes while treatment stays the same.

Dose-sensitive measures answer a somewhat different question from fixed list-based scales. The Drug Burden Index incorporates prescribed dose relative to a minimum efficacious dose and also includes sedative exposure. Geßele et al. (2024) showed that dose-related and non-dose-related approaches did not represent perioperative exposure in the same way when postoperative delirium was examined. Dose information may make a measure more responsive to dose reduction, but it also introduces assumptions and data requirements that are not available in every setting. Because DBI covers a broader construct than anticholinergic-specific scales, better performance on a particular outcome should not be interpreted automatically as better measurement of the same exposure.

The data source can shape instrument choice before clinical validity is considered. Claims analyses in Germany and Slovenia show how large populations can be classified efficiently with list-based approaches (Cebron Lipovec et al., 2020; Reinold et al., 2021). Yet administrative data usually

record prescribing or dispensing more reliably than actual use, dose changes, or symptoms. Srikartika et al. (2025) found that some scales translate more readily into routinely collected data than others. A simple measure can therefore become dominant because it is computable, not because it is necessarily the best representation for bedside medication review. This distinction matters when results from large databases are later used to justify clinical thresholds: feasibility at population scale and usefulness for an individual medication decision are different properties.

Reproducibility, cross-scale agreement, and biological validity are separate measurement properties. A scale can give a stable result when applied repeatedly to the same data and still disagree systematically with another instrument because their drug lists or weights differ. High concordance between two similarly constructed scales does not establish that either reflects a true biological quantity. Recent reviews are consistent on this point: anticholinergic burden scores are constructed indicators of exposure, and there is no routine external criterion that resolves disagreement between them (Lisibach et al., 2021; Vennard et al., 2026).

2. Outcome-Specific Predictive Validity of Anticholinergic Burden Measures

Outcome association is the most common form of clinical validation, although it answers less than is sometimes assumed. Lisibach et al. (2022) compared 19 burden scales in older inpatients and found that high scores on several measures were associated with in-hospital mortality. The proportion of patients classified as highly exposed varied considerably between instruments. A scale can therefore identify a group with higher event rates while flagging a very different number of patients from another accepted scale. The association is relevant, but it does not tell a pharmacist how accurately the score separates one patient who will experience harm from another who will not. That distinction becomes important as soon as burden values are used for prioritisation rather than epidemiological description.

Cognitive studies show the gap between association and individual prediction particularly clearly. Tristancho-Pérez, Villalba-Moreno, López-Malo de Molina, et al. (2022) compared burden measures against cognitive impairment in complex chronic patients. Only the Drug Burden Index showed statistically significant discrimination, and the area under the curve remained weak. Bishara et al. (2020) reported associations between the Anticholinergic Effect on Cognition scale and mortality, hospitalisation, and cognitive decline after dementia diagnosis, whereas a Cochrane prognostic review judged the certainty and consistency of evidence insufficient for strong individual prediction in mild cognitive impairment or dementia (Taylor-Rowan et al., 2022). Baseline cognition, neurodegenerative disease, depression, concurrent sedative exposure, and multimorbidity all influence the same outcomes and can partly explain why discrimination remains limited even when the exposure-outcome association is genuine. Group-level association can therefore coexist with poor patient-level classification without either result being internally inconsistent.

Falls create the same problem in a more obviously multifactorial outcome. Stewart et al. (2021) found that anticholinergic burden measures were associated with falls across the prognostic literature. Dinh et al. (2023) then tested whether burden scores improved a multivariable model in adults with polypharmacy. The additional predictive information was small and weakened in external validation. Anticholinergic exposure may still contribute to risk, but age, previous falls, morbidity, mobility, and other routinely available variables can already account for much of the variation that the score appears to capture. A burden measure may therefore remain clinically relevant as one modifiable exposure while contributing little to the performance of a general fall-risk model.

Effect size and model performance deserve more attention than a significant p value. Lavrador et al. (2021) found that associations between burden tools and adverse outcomes were often weak to fair. Large samples can make a small association statistically convincing without making it useful for clinical classification. Srikartika et al. (2026) took the harder step of comparing six scales for anticholinergic-related hospitalisation and emergency visits with temporal validation. The Korean Anticholinergic Burden Scale performed somewhat better in parts of the analysis, but differences were modest and changed with the endpoint. Discrimination and calibration did not identify one scale that was consistently superior. This type of study is more informative for clinical use than a simple association because it asks whether the score behaves acceptably when transported forward in time and whether predicted risks correspond to observed events.

Acute settings add time-dependent vulnerability that many scales were not designed to represent. Geßele et al. (2024) compared dose-related and non-dose-related burden measures in

postoperative delirium. Surgery, anaesthesia, acute pain treatment, sleep disruption, and physiological stress change baseline risk over a short period. The relative contribution of one medicine can also change as renal function or co-medication changes. Scale performance therefore depends partly on population, time horizon, and outcome.

DBI requires another qualification because it captures sedative exposure as well as anticholinergic load. Its dose-sensitive structure can be useful when dose reduction is the intervention, but comparisons with ACB or other anticholinergic-specific scales do not represent alternative measurements of an identical construct. Better performance may reflect the broader construct itself, especially for outcomes influenced by sedation as well as muscarinic antagonism. A universal ranking is difficult to defend on that basis.

Taken together, the prognostic literature supports use of burden scores as risk markers more strongly than as individual risk calculators. Higher values repeatedly identify populations with poorer outcomes, but discrimination is usually modest and the incremental value beyond routine clinical variables is often limited. Performance also changes with the endpoint, population, and period of follow-up. A high score can reasonably raise the priority of a medication review when the clinical setting makes anticholinergic harm plausible. It should not be communicated as though it were a calibrated probability that a particular patient will fall, develop delirium, or experience cognitive decline, because most scales have not demonstrated that level of predictive performance.

3. Clinical Decision-Support Utility in Medication Review and Deprescribing

A high burden value can identify a regimen that deserves closer examination, but it cannot identify the medicine that should be changed. The contributing drug still has to be considered in relation to its indication, the amount of exposure, the plausibility of current symptoms, and the likely consequence of modification. Hilmer and Gnjidic (2022) describe this gap between a research measure and its use in practice. The most plausible clinical role of the score is therefore decision support: it can change which medication lists are examined first and make cumulative exposure less easy to overlook. That role is useful even when the score is not sufficiently accurate to function as an individual risk estimate.

Evidence that score reduction improves patient outcomes is considerably less secure. Braithwaite et al. (2023) reviewed randomised interventions intended to reduce anticholinergic medication burden in older adults and found no clear improvement in falls, cognition, or quality of life across a small and heterogeneous trial base. The interventions differed in who delivered the review, how medicines were selected, and whether prescribers accepted recommendations. Those differences make it difficult to attribute a null downstream result to the burden concept itself. The review nevertheless shows that lowering a numerical score is not the patient outcome that matters and that broad clinical endpoints may be difficult to change within short medication-review studies.

Cochrane evidence on anticholinergic deprescribing for prevention of cognitive decline or dementia reached a similarly cautious conclusion (Taylor-Rowan et al., 2023). Some medicines cannot be withdrawn safely, and cognitive outcomes may require longer observation than most medication-review trials provide. Deglow et al. (2024), in contrast, illustrates the narrower operational value of pharmacist-driven deprescribing in veterans with dementia. A burden measure can support case finding, identify a contributing medicine, and structure a recommendation that is then reviewed with the prescriber and followed after the change. In practice, that sequence may reveal a drug with a weak indication, a dose that can be reduced, or a patient whose symptoms warrant closer monitoring even when deprescribing is not chosen. It may also expose situations where no medication change is appropriate, which is clinically relevant because score reduction is not a legitimate goal by itself. This is evidence that burden measurement can be embedded in pharmacy workflow, but it remains different from evidence that the workflow reduces long-term cognitive or functional harm.

Low scores should not reassure a clinician when the pharmacology in front of them suggests an adverse drug reaction. Pecquet et al. (2026) identified reported anticholinergic reactions involving medicines that common scales did not always classify strongly. New confusion or urinary retention, for example, may justify review of a plausible drug-event relationship even when cumulative burden is low. The reverse is also important. A high score without a clinically plausible problem or a safer feasible alternative does not create an automatic indication to deprescribe. Clinical suspicion and burden measurement should inform each other rather than operate as competing rules.

Choice of instrument should follow the decision and the available data. Services working from claims records may need a scale that can be calculated consistently from sparse information. A memory clinic may value cognitive orientation and local drug coverage, as the Swe-ABS comparison suggests (Rube et al., 2026). Dose-adjustment programmes may prefer a dose-sensitive measure. The same service can reasonably use different tools for population case finding and bedside review if the purpose is explicit.

The evidence supports a narrower form of clinical utility than is sometimes implied by the phrase. Anticholinergic burden scores can prioritise review, make cumulative exposure visible, and provide a reproducible starting point for discussion. They can also help services audit how often high-burden regimens are reviewed or whether recommendations change prescribing. Whether the resulting recommendation should involve withdrawal, substitution, dose reduction, closer monitoring, or no change depends on the medicine and the patient rather than on the total score. Direct evidence that score-guided decisions improve clinical outcomes remains limited, so practical actionability, prescribing change, and proven patient benefit should not be treated as the same endpoint.

4. Translational Implications for Scale Selection, Thresholds, and Validation

Scale variability has an immediate consequence for research and practice: an anticholinergic burden value is not fully interpretable without knowing how it was produced. The plurality of scales is not entirely a defect, because instruments differ in purpose, available drug coverage, and the data they require. Problems arise when studies or services report “high burden” as though accepted tools were interchangeable. The concordance work of Tristancho-Pérez, Villalba-Moreno, Santos-Rubio, et al. (2022) and the comparison of Swe-ABS with ACB by Rube et al. (2026) show that instrument choice can alter who is classified as exposed enough to attract attention. For comparative research, the scale should therefore be treated as part of the exposure definition rather than as a neutral calculator applied after the exposure has already been defined.

Reproducibility, cross-scale agreement, and biological validity need to remain separate in the language used around these tools. A stable score is not necessarily complete if the drug list is outdated, and agreement with another scale is not a biological reference standard. The absence of an accepted external criterion explains why the search for a single “most reliable” scale has been unproductive. Contemporary reviews instead point toward explicit reporting of the instrument, its intended construct, and the population in which its performance has been tested (Lisibach et al., 2021; Vennard et al., 2026). The distinction also matters for quality improvement: a service can reproduce the same score perfectly and still base decisions on a classification system that is poorly aligned with its formulary or outcome of concern.

The same discipline is needed when outcome evidence is interpreted. Association identifies a risk marker; prediction requires useful discrimination and calibration, preferably tested outside the dataset in which the model was developed. Dinh et al. (2023), Tristancho-Pérez, Villalba-Moreno, López-Malo de Molina, et al. (2022), and Srikartika et al. (2026) all show why this distinction matters. Burden scores may be statistically related to clinically important outcomes while adding little information for classifying an individual patient. The difference is not semantic. A service deciding whom to prioritise for review needs to know how many patients a threshold will flag and how often those patients actually experience the outcome, not only whether the mean score is higher in an adverse-outcome group. This does not invalidate the exposure signal; it limits the claim that can be made from it.

Clinical pharmacy sits one step further downstream. A score becomes useful when it changes attention or prompts a pharmacological question that would otherwise be missed. Evidence that it improves patient outcomes after guiding treatment is much thinner. For that reason, a service should be able to state what the score is expected to do, what threshold triggers review, and what clinical assessment follows the trigger. A burden measure used for population case finding may be valuable even if it is too imprecise for automated deprescribing, while an intervention trial must show more than a fall in the score itself. These different claims are set out in Table 1; they should not be used as substitutes for one another.

Table 1 Analytical Distinction Between Three Claims Made From Anticholinergic Burden Scores

Claim	Evidence that supports it	What it does not establish	Clinical pharmacy interpretation
Cross-scale agreement	Concordance, classification consistency, drug-list overlap	Biological accuracy or superiority of one instrument	Recognise how scale choice changes who is flagged
Predictive validity	Association, discrimination, calibration, external or temporal validation	A calibrated individual probability of harm unless prediction has been demonstrated	Use outcome-specific evidence when prioritising review
Decision-support utility	Whether score-guided review changes attention, prescribing, or patient outcomes	That a high score alone identifies a medicine that should be stopped	Treat the score as a trigger for pharmacological review, not a prescribing instruction

Thresholds make cross-scale differences operational. If one electronic system labels a regimen high burden and another does not, the patients selected for review will differ before any pharmacist has examined the medicines. A universal scale is not the only possible solution. Transparent local choice may be more defensible when the instrument matches the formulary, the available data, and the clinical purpose. Services should also know whether a threshold was validated for the outcome they care about or adopted because it is conventional. A cut-off developed for one population can become misleading when transferred to another setting with different prescribing patterns and baseline risk. The threshold is best treated as an entry point into review rather than an automatic prescribing instruction.

The intervention literature also places a boundary around clinical utility. Braithwaite et al. (2023) and Taylor-Rowan et al. (2023) found considerable uncertainty around downstream benefit from anticholinergic deprescribing interventions. At the same time, clearly unnecessary exposure can still warrant attention, and adverse reactions cannot be ruled out by a low cumulative score. The pharmacovigilance findings of Pecquet et al. (2026) are important here. A single drug can produce a clinically plausible anticholinergic event even when a burden scale is reassuring, while a high total may be acceptable when contributing medicines remain necessary and well tolerated. The score is therefore most useful when it widens pharmacological attention without becoming a gatekeeper for symptoms or a substitute for judgement.

Country-specific scale development addresses a real weakness in older lists. KABS, CRIDECO, and Swe-ABS revised drug coverage for prescribing environments not fully represented by established instruments (Hwang et al., 2021; Ramos et al., 2022; Rube et al., 2023). Agreement with an older scale is informative but cannot establish superiority. Independent outcome validation is more useful, particularly when a new instrument changes the proportion of patients classified as high burden.

Large administrative datasets make temporal and external validation feasible, but a claims-derived score is still a proxy for exposure. Dispensing does not guarantee ingestion, dose changes may be incompletely represented, and symptoms are often unavailable. Clinical datasets contain richer patient information but are smaller and more selective. Future validation needs both perspectives: accurate medication exposure, clinically specific outcomes, discrimination and calibration, and testing outside the original sample. A particularly useful design would follow score-guided pharmacist review through to the prescribing decision and then to an outcome that is plausibly related to the medicine changed. It should also record whether recommendations were accepted and whether exposure actually changed, because failure at either step can make an otherwise reasonable intervention appear ineffective. That sequence would separate three stages that are often merged in the literature: identifying a high-burden regimen, modifying treatment, and demonstrating patient benefit. Without it, clinical utility remains partly inferred from measurement and association studies rather than demonstrated directly.

This review was structured but not exhaustive, and the 2020-2026 literature is heavily weighted toward older people, dementia, and polypharmacy. The implications are therefore better supported in

those populations than in younger patients with short medication lists. Direct comparison is also complicated by genuine construct differences, especially when DBI is placed beside anticholinergic-specific scales. These limits make the intended use, outcome, and level of inference more important than a universal ranking.

CONCLUSION

Anticholinergic burden measurement is useful in clinical pharmacy because it makes cumulative exposure easier to recognise, but the resulting value remains instrument-dependent. Recent evidence shows persistent variation in drug coverage and scoring assumptions, and accepted scales do not classify the same regimen consistently. Higher burden is often associated with adverse outcomes, yet individual predictive performance is usually modest and depends on the population, endpoint, and competing clinical information. Those limits are especially important when thresholds are used to select patients for review.

The most defensible use of these tools is decision support rather than automated prescribing. A burden score can prioritise medication review and draw attention to exposure that deserves pharmacological assessment, particularly in older and polypharmacy populations where the evidence is strongest. It cannot determine by itself which medicine should be withdrawn or whether changing treatment will improve a patient outcome. Future studies should test scale performance against clearly defined outcomes, report discrimination and calibration when prediction is claimed, and follow score-guided pharmacy interventions far enough to show whether medication changes produce benefits beyond a lower numerical burden.

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