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## **Complexity of medication regimens: Epidemiology, patient perception, and opportunities for complexity reduction**

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In recent years, the complexity of medication regimens has gained attention in medical research because of its negative impact on adherence. While numerous factors adding to the complexity of taking medicines correctly and timely have been identified there is still no universally accepted definition of medication complexity at hand. Current definitions are diverse and, hence, study results of limited comparability. In these definitions medication regimen complexity may refer to the number of medications or daily administrations of distinct drugs, to application of demanding dosage forms (e.g. inhaler, eye drops, or syringes for subcutaneous injection), special directions to be followed (e.g. food-dosing restrictions), or challenging drug handling (e.g. tablet splitting). On the other hand to successfully perform a specific drug therapy different cognitive and functional abilities of the executing patients are required; they must remember drug intake, read medication chart and brand names, and correctly apply different dosage forms. As a consequence individual perception of medication regimen complexity will significantly differ. Therefore two different strategies to reduce medication regimen complexity will be necessary. A first strategy is to eliminate medication regimen characteristics related to complexity and nonadherence irrespective of the skills and aptitudes of the patients (primary prevention). A second and complementary strategy is to identify patients having difficulties with medication management and to subsequently offer tailored solutions such as the use of application aids or just guarantee that there is another person providing the necessary support (secondary prevention).

Therefore, the aim of this work was to evaluate patients' preferences related to different medication regimen characteristics and to compare them with characteristics known to influence adherence to drug therapy. Subsequently, the prevalence of medication characteristics potentially impairing adherence was evaluated, strategies to reduce these characteristics were developed, and their potential impact on actual drug regimens of patients at discharge from a tertiary care hospital was assessed. To facilitate the adoption of such strategies into daily routine, this work evaluated whether simplification strategies can be translated into an algorithm-based approach that can be integrated into a clinical decision support (CDS) system. The last aim of this work was to evaluate an instrument to identify

patients who are likely to fail when complex medication regimens have to be followed. Hence, the Timed Test of Money Counting (TTMC) was prospectively evaluated as an easy to perform instrument to identify patients with restricted medication management capacity (MMC).

This work demonstrated that only about one in four patients are able to state clear preferences or dislikes with regard to their medication regimen characteristics. However, clear statements matched findings from former adherence studies, indicating that also preferences will likely correlate with adherence to drug therapy. Evaluation of individual preferences before starting new therapies might therefore be a promising way to prevent nonadherence. Concurrently, in more than 90% of the patients at least one medication regimen characteristic known to reduce adherence was prevalent. Indeed, numerous simplification strategies for such characteristics are already known and would allow for reducing or avoiding almost one fifth of these characteristics. Substitution of multiple single drug prescriptions by fixed-dose combinations and the switch from prescribed tablet splitting to non-split intact tablets with the required strength were two strategies that emerged as straightforward options for integration into an electronic CDS system. Therefore, two algorithms were developed that combined prescribing data with data from the German drug market and brand-specific information from existing local knowledge bases. To pilot the feasibility of the overall approach and stimulate refinement of the algorithms a draft version of the algorithms was transferred into an electronic CDS and integrated into an electronic prescription platform to assist physicians in simplifying medication regimens. In the final study, aimed to identify patients who cannot cope with complex medication regimen, the TTMC was evaluated. Interestingly and unexpectedly, the required time during TTMC performance was not correlated with the number of errors while filling a daily pillbox. However, the TTMC identified patients with high risk for errors in pillbox filling (TTMC > 70s; positive predictive value = 75) and might therefore be a useful rapid tool to categorize a patient's MMC. Nevertheless, the TTMC is not an appropriate instrument to comprehensively assess patients' MMC, because it likely depends on several factors such as visual and cognitive functions and the TTMC is not appropriate to evaluate the interaction and quantitative effect of distinct modulators.

In summary, reduction of medication regimen characteristics which are known to jeopardize patients' adherence is possible. Corresponding tools to simplify medication regimens can be implemented as CDS system to assist physicians at the point of prescribing. On the other hand suitable instruments to evaluate patients' medication management capacity in daily routine are still missing.