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The Impact of Cognitive Function on Medication Management: Three Studies

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Abstract

OBJECTIVE: Medication non-adherence has been a persistent problem over the past 3 decades; forgetting and being distracted from regular routines are the barriers most frequently cited by patients. Prior research on cognitive function and medication adherence has yielded mixed results. This report compares findings of 3 studies.

DESIGN: All were longitudinal; two were randomized controlled intervention trials, one was descriptive. Samples of adult patients taking once daily lipid-lowering medication, diabetic patients with co-morbid conditions on complex regimens, and early-stage breast cancer patients on hormonal therapy completed similar batteries of standardized, valid neuropsychological tests at baseline.

MAIN OUTCOME MEASURES: Adherence to medication regimens, over time, was tracked with electronic event monitors.

RESULTS: Medication non-adherence was prevalent in all studies. Deficits in attention/mental flexibility and/or working memory predicted non-adherence in all studies; impaired executive function was related to poor adherence in 1 study.

CONCLUSION: These findings suggest that better mental efficiency may be the key to better medication adherence with any regimen and that targeted cognitive functions, which can be easily and quickly assessed, may identify patients at risk of poor adherence regardless of diagnosis or regimen.

Keywords

medication adherence; cognitive function

Introduction

There is compelling evidence that patients with chronic illness are not adhering to treatment regimens as prescribed in the United States and around the world (National Council, 2007). Non-adherence has been a recognized, persistent problem over the past 3 decades despite numerous informational, educational and behavioral interventions to promote better patient compliance, particularly with medications (Dunbar-Jacob et al., 2000; Kripilani, Yao, Haynes 2007). Our aging population, with increasing numbers of co-morbid chronic illnesses and comparably complex medication regimens, is at risk of poor physical and emotional health

outcomes and marginal quality of life due to difficulty with adherence to medication regimens (Higgins & Regan, 2004; Insel, Morrow, Brewer, Figueredo, 2006). Health outcomes and costs of health care are clearly related to the degree that patients follow their treatment regimens (Dunbar-Jacob, 2005). Poor adherence is estimated to cost approximately $177 billion in total direct and indirect (such as lost wages, lowered productivity, quality of life) costs (National Council, 2007).

Medication adherence is complex behavior, related to and dependent upon many intrinsic (patient) and extrinsic (contextual) factors (DiMatteo, 2004). Adherence to prescribed medication requires a complex management process: scheduling, adjusting to schedule changes, planning for availability of medication, remembering past events, problem solving around missed/late doses. Nearly 50% of persons with chronic disorders who manage long term medication regimens have problems adhering satisfactorily (Dunbar-Jacob et al., 2000). The question arises as to whether cognitive function plays a role in medication adherence.

Forgetting and being distracted from one's regular routine are the barriers to medication non-adherence most frequently cited by patients (e.g. Burra et al., 2007; Wagner & Ryan, 2004). Many chronic diseases, such as diabetes and hypertension, increase risk of cognitive decline by middle-age (e.g. Ryan & Geckle, 2000; Waldstein, Brown, Maier, Katzel, 2005). Medications, such as those used in cancer care, also impact on cognitive ability (Bender et al., 2007). Research on cognitive function and medication adherence has focused on disease specific samples with diverse aims and mixed methodologies and has yielded mixed findings to date (e.g. Barclay et al., 2007; Schutte, 2006; Rosen, 2003).

In this pooled analysis, we ask the question “Are there common aspects of cognitive function that impact on medication adherence across diagnoses and regimens?” We report on findings of 3 studies among adult patients with diverse diagnoses and medication regimens. Cognitive function was assessed with similar batteries of neuropsychological tests; adherence to medication taking was assessed with identical analyses of electronically monitored event data.

Methods

Studies were conducted by researchers at the Center for Research in Chronic Disorders (CRCD) (P30 NR003924) in the University of Pittsburgh's School of Nursing. Neuropsychological assessment was designed and supervised by directors of the Cognitive Core of the CRCD; statistical analyses were performed or supervised by the director of the Data Management and Analysis Core of the CRCD. Institutional Review Board approval was obtained prior to conduct of each study. All subjects signed informed consent prior to enrollment.

All subjects resided in the greater Pittsburgh area. Sociodemographic characteristics of subjects in the three studies are illustrated in Table 1.

Adherence to a medication regimen in each study was tracked with electronic monitoring devices (AARDEX electronic medication event monitoring system “MEMS”). Subjects were given a cap containing an electronic monitoring device and pill bottle for each medication, with detailed instructions for use at the baseline session. Subjects were instructed to keep tablets in the pill bottle and were told that there is a counter in the medication cap and to open the bottle only to dispense the correct dose (they were advised to refill bottles at a regular dosing time to avoid falsely triggering the counter). When the caps were returned after the monitoring period, data stored on the microchip was downloaded into an ASCII text tile which was then imported into a data management program. Data included cap openings (date and time) so that adherence to dose and to inter-dose interval could be tracked for the entire study period.

Medication adherence was assessed continuously in all studies. Adherence data was aggregated over one month intervals and/or at the key assessment points (baseline and 6 months in studies #1 and #3; baseline in study #2). For aggregated adherence data, summary indices were computed in terms of the percentage of prescribed doses taken, percentage of days with correct intake, percentage of doses with optimal timing, percentage of days with correct intake and timing of doses.

Cognitive function was assessed with similar batteries of neuropsychological tests in all studies. Test batteries are illustrated in Table 2, individual tests are described in the appendix, preceding the reference list. All subjects completed assessments, administered and scored by trained technicians who were supervised by a licensed neuropsychologist, at baseline. Studies #1 and #3 used individual tests to represent domains of function, study #2 used domain of function scores in this pooled analysis. Predictive relationships between individual tests or domains of cognitive function at baseline and medication adherence data were determined with hierarchical regression analyses in all studies. A significance level of $p<.05$ was used for studies #1 and #2; significance of $p<.10$ was used in study 3 because of the small sample size.

Study #1

This was a secondary analysis of data from the ACT/Care study, a longitudinal randomized controlled trial (RCT) of patients being treated for hyperlipidemia. The sample consisted of 157 generally healthy adults, aged 24 to 60, with LDL serum cholesterol levels of ≥160mg/dl. Socio-demographic characteristics of subjects are illustrated in Table 1.

Patients were randomly assigned to a newly prescribed drug (Lovastatin, 20mg) or placebo to be taken once a day at bedtime; medication adherence was monitored for 24 weeks.

Cognitive function was assessed with a test battery designed in the mid 1990's, prior to the emergence of evidence that working memory and executive function appear to be important cognitive abilities with regard to medication adherence (Insel, 2006; Park, 1999, 2007). Trails B and Digit span back assess abilities similar to those needed for newer tests more specific to working memory, are highly correlated with tests of working memory in study #2 and, thus, were used to represent that domain of function in this analysis.

Study #2

The Diabetes Management Study was an RCT to evaluate the effect of a problem solving based intervention to improve medication adherence. Three hundred fifty-four adults diagnosed with Type 2 diabetes, hypertension, and/or hyperlipidemia were recruited from primary care practices, had been in the clinic practice for at least 12 months and were taking prescribed oral medications for at least two of the targeted conditions. Subjects had 2-15 diagnosed co-morbid conditions (including the target diagnoses) with a mean of 5.6 ± 2.81 illnesses.

Cognitive function was assessed with a comprehensive test battery that was reduced to domain scores by factor analysis of baseline neuropsychological test data (see Table 2). Raw scores for each test (see appendix) were converted to T scores, summed, and averaged to create domain scores used in these analyses. Medication adherence data for the phase 1 screening period of 24 days was assessed for this report.

Study #3

The primary aim of the Anastrozole Use in Menopausal Women (AIM) study is to examine the effect of the hormonal agent, anastrozole, on cognitive function in women with early stage breast cancer. A secondary aim of this study is to explore whether cognitive impairments predict non-adherence to anastrozole in this sample. Thirty-four women with stage I, II, or IIIa

breast cancer with no prior cancer diagnosis and no history of substance abuse, neurologic disease or hospital admission for psychiatric illness in the two years prior to study enrollment participated in this phase of the study.

Cognitive function was assessed with a comprehensive battery (Table 2) prior to the initiation of anastrozole therapy and then at six months post-initiation of therapy. Adherence to anastrozole therapy was assessed continuously for the first six months of therapy. Subjects were also asked to disclose reasons for non-adherence to anastrozole.

Results

A total of 581 adults comprised the samples across the three studies (Table 1) with most subjects being well-educated, white women. Subjects with hyperlipidemia were younger, more likely to be married, and more often employed than in the other studies.

Non-adherence with medications across all studies was prevalent. Percentage of adherence to number of doses prescribed and percentage of days adherent to prescribed dose (correct intake), prescribed inter-dose interval, and to the dose and interval in each study are reported in Table 3. Across all studies mean adherence decreases from percentage of prescribed doses taken to days with the correct dose, to prescribed inter-dose intervals, to days with the correct number of doses and intervals.

Regression analyses (results reported in Table 4) determined that cognitive function predicted non-adherence in all three studies with attention/psychomotor speed being the domain that most consistently predicted medication adherence across all three studies. A test of mental flexibility/working memory (Trails B) predicted percentage of days adherent to the correct dose, to the near-optimal inter-dose interval, and to percentage of days with both the correct dose and interval over 24 weeks in the hyperlipidemia sample. Among subjects with diabetes, only the domain of attention/psychomotor speed predicted adherence to the percentage of prescribed doses. In the study of patients with early stage breast cancer, tests of attention (Digit Vigilance time) and executive function (CANTAB SOC) predicted adherence to the percentage of prescribed doses taken, percentage of days with the correct dose, and percentage of days with the correct inter-dose interval; verbal learning and memory (CANTAB PAL) predicted adherence to the percentage of prescribed doses over a 24 week period.

Discussion

This report provides preliminary evidence that similar aspects of cognitive function do predict medication adherence across diagnoses, regardless of regimen complexity. These findings are potentially significant to researchers and clinicians in that they reveal mental processes that are may be vital to taking all medications, even over short periods of time.

Remembering to take medications as directed, despite distractions inherent in busy and often unpredictable lifestyles, is behavior dependent on the ability to plan and perform multiple tasks simultaneously and/or sequentially. Attention refers to different abilities related to receiving and processing information: it is most generally conceptualized as focused attention or vigilance and shifting attention, or mental flexibility. Working memory is the ability to hold information in short term memory and process it despite distraction; it is crucial to successful multi-tasking. Abilities driven by executive function are problem solving, planning and organizing schedules, inherent in developing a plan to adhere to medication regimens (Burra et al, 2007; Lezak, 1995).

Attention, working memory, and executive function are cognitive abilities representative of fluid intelligence and are indicative of mental efficiency. These are complex processes that

rely on the integrity of interconnected areas of the brain (Ryan et al., 2006). Working memory has been the most extensively studied of these functions; one of the most sensitive tests currently available is Letter Number Sequencing used in the Diabetes Management Study. Trails B and Letter-Number Sequencing were strongly correlated ($p<.000$) in that study; this supports the premise that we are measuring the same construct with different instruments in these analyses. The most often cited model of working memory proposes a series of buffers responsible for storing information, with rehearsal and executive function processes that keep accessible and manipulate the information (Baddeley, 2001). A more recent theory of working memory suggests that attention, working memory, and executive function are interdependent tasks (e.g. Wager, Jonides, Smith, Nichols, 2005). This theory hypothesizes that information from the visual external world is processed and stored in the parietal and temporal lobes while information stored in long term memory is accessed from the frontal cortex. Selective attention modulates incoming information, executive processes that regulate use of the information, rehearsal, and storage are controlled by the same structures that modulate control of that information (Jonides, Lacey, Nee, 2005). In short, mental efficiency relies on the integrity and inter-connectedness of frontal, temporal, and parietal lobe cortical structures.

The primary limitations to this report are lack of a measure of executive function in the hyperlipidemia study, the short period of adherence monitoring in the diabetes study, and the small sample size in the study of breast cancer patients. These short-comings are offset by the fact that all studies did use comparable measures of cognitive function and electronic monitored medication adherence and similar analytic strategies which allowed us to compare results across studies. We also note limitations of electronic event monitoring (EEM); the most relevant being the assumption that each cap opening represents a single pill taking which is not always the case. A specific limitation in these studies was absence of medication diaries to allow subjects to report unintended or missed openings (e.g. for pocket dosing, pill minder filling). Limitations and strengths of EEM have been discussed in previous reports which note that there is no single optimal method for tracking medication taking (Chesney, 2006). Adherence researchers also note that electronic monitoring, despite its limitations, provides objective, more valid, rich longitudinal data than other methods such as self reports, pill counts when the focus is on prospective adherence to medications (e.g. Fennie, Bova, Williams, 2006).

More research is needed to support and confirm these findings; we recommend and intend to conduct future collaborative efforts to investigate predictive relationships between domains of cognitive function and adherence with medication and other health promotion regimens across populations and disciplines. Our goal is to pinpoint a simple, easily and quickly administered test of mental efficiency that reliably identifies patients at risk of non-adherence and to develop interventions to promote adherence which minimize or circumvent the need for that ability. That would enable clinicians to determine which patients may need extra attention, such as using pill minders and/or linking medication taking to performance of every-day tasks.

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Appendix

Learning and Memory

Verbal list learning and memory were assessed with the total for 5 learning trials and the delayed recall trial of the Rey Auditory Verbal Learning Test (RAVLT). Story learning and memory for contextual material were assessed with Logical Memory 1 and 2 from the Wechsler

Memory Scale, 3rd Ed. (WMS-3) (Wechsler, 1997). Non-verbal learning and memory were assessed with the immediate and delayed recall trials of the Rey Complex Figure Test (RCF) by measuring ability to retain and recall drawing of a geometric figure. Recall of the location of a series of visual designs presented in boxes on a computer screen is assessed in the CANTAB PAL. The Rivermead Story Delayed Recall requires subjects to recall details from two paragraphs 20 minutes after they were read aloud to them.

Attention and Psychomotor Speed

Time to complete Digit Vigilance assessed ability to quickly scan 2 pages of numbers for targeted items, time to finish Trails A assessed ability to efficiently connect numbers in sequence. Trails B time assessed ability to efficiently alternate between sequential lists of numbers and letters. Digit Symbol from the WMS-3 required visual scanning and rapid response in substituting numbers for symbols according to a learned code. Grooved pegboard assessed psychomotor speed and manual dexterity with both hands. The RVIP requires individuals to press a computer mouse each time designated strings of numbers appear on a computer screen.

Working Memory

Working memory was assessed with the forward and back trials of Digit Span (WMS-3) by measuring ability to retain and reverse increasingly long series of numerals. Letter Number Sequencing from the WMS-3 provided a measure of working memory by assessing ability to retain and manipulate sequences of numbers and letters. The CANTAB SWM requires subjects to search for blue tokens by touching a computer screen to open a number of colored boxes and reveal their contents.

Visual-spatial/Constructional ability

The Rey Complex Figure copy task assessed ability to replicate a complex geometric figure. Block Design (Wechsler Adult Intelligence Scale, 3rd Ed; WAIS-III) (Wechsler, 1997) assessed ability to reproduce two dimensional geometric figures with colored blocks. Ability to manually replicate a visual-spatial sequence of locations was assessed with Spatial Span (WMS-3). Object Assembly (WAIS-III) assessed visuo-spatial organization and problem solving by requiring subjects to assemble puzzles representing familiar objects. The Embedded Figures test assessed visual-spatial analytic ability with a verbal rather than a motor response.

Language

Semantic fluency was assessed with the Controlled Oral Word Association (COWA) test which required subjects to produce words with a designated first letter and a list of animals with one minute allowed for each task. The category (animal) trial is also considered to be a measure of executive function.

Executive Function

The Stroop Interference test evaluated the ability to inhibit an over-learned response (reading) quickly by naming the color of ink rather than speak the printed word. The four conditions of the Delis Kaplan Color-Word Interference Test include 1) subjects say the color of patches printed on a page, 2) subjects are presented with a page of color words printed in black ink and are asked to read the words, 3) subjects are presented with a page of color names printed in different colored ink and are asked to name the ink color, and 4) subjects are presented with a page of words some of which are printed in a different colored ink and some of which are inside

a box. Subjects are asked to name the ink color of words unless the words are inside a box and in that case, they are asked to read the word in the box. In the CANTAB SOC subjects to are presented with 3 colored balls arranged in 3 hanging pockets. They move the balls in one of these arrangements, according to specified rules, to match the other arrangement.

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Table 1

Sociodemographic Characteristics of Subjects

	Hyperlipidemia study (n = 174)	**Diabetes Study (n = 373)**	**Breast Cancer study (n = 34)**
Age: years (mean ± s.d.)	46.2 ± 8.7	63.7 ± 10.3	59.88 ± 4.8
Gender (F)	45.9%	59.5%	100%
Race (White)	88.5%	81.4%	100%
Married	61.2%	55.2%	61.8%
Education: years (mean, s.d.)	15.3 ± 3.1	14.4 ± 3	14.92 + 2.8
Occupational Status (currently employed full or part-time)	77.7%	29.2%	NA

NA=Not Available

Table 2

Measures of Cognitive Function

	Hyperlipidemia Study	Diabetes Study	Breast Cancer study
Attention/Psychomotor Speed	Digit Vigilance total errors	Trails A & B, Digit Symbol Substitution[3], Digit Vigilance total time, Grooved Pegboard	CANTAB RVIP[5] Digit Vigilance total time Digit Symbol Substitution[3] Grooved Pegboard
Learning & Memory	RAVLT[1] delayed recall RCF delayed recall[2]	RAVLT & Logical Memory (WMS-3)[3]	CANTAB PAL[6] RAVLT immediate & delayed recall, Rivermead Story delayed recall RCF immediate & delayed recall
Visuo-Spatial/Constructional Ability	RCF copy	RCF immediate recall, Block Design[4], Spatial Span[3], Object Assembly[4], Embedded Figures	RCF copy
Mental Flexibility/Working	Trails B	Letter-Number	Trails B
Memory	Digit Span back	Sequencing[3], Digit Span[3]	CANTAB SWM[7]
Executive Function	Not Available	Stroop Test	COWA[8] Delis Kaplan CWIT[9] CANTAB SOC[10]

[1] Rey Auditory Verbal Learning Test

[2] Rey Complex Figure Test

[3] Wechsler Memory Scale, 3rd Ed.

[4] Wechsler Adult Intelligence Test, 3rd Ed

[5] CANTAB = Cambridge Neuropsychological Test Automated Battery; RVIP = Rapid Visual Information Processing

[6] PAL = Paired Associate Learning

[7] SWM = Spatial Working Memory

[8] Controlled Oral Word Association

[9] Color Word Interference Test

[10] Stockings of Cambridge

Table 3

Adherence to medication

	Hyperlipidemia Study (24 weeks)		Diabetes study (24 days)		Breast Cancer Study (24 weeks)	
	Range	**mean ±, s.d.**	**Range**	**mean ±, s.d.**	**Range**	**mean ±, s.d.**
% Prescribed number of doses	0-108.9	81.1± 26.7	0-159	92.6± 17.6	14.0-105.4	84.0± 28.2
% Days with prescribed dose (correct intake)	0-97.6	70.7± 25.5	0-100	82.2± 22.4	14.0-100	81.6± 28.3
% Days with correct inter-dose interval	0-97.6	61.75± 27.2	0-100	64.2 ± 30.1	0-100	78.7± 31.4
% Days with correct dose and interval	0-95.2	57.5± 26.4	NA		0-99.4	77.1± 30.8

NA=Not Available

Table 4

Summary of regression analysis results across studies (variables that entered the final model)

	Hyperlipidemia Study N=157			Diabetes Management Study N=354		Breast Cancer Study N=34		
	% days with correct dose	% days with optimal inter-dose interval	% days with correct dose & optimal inter-dose interval	# of prescribed doses	% days with correct dose	# of prescribed doses	% days with correct dose	% days with optimal inter-dose interval
Attention/Psychomotor speed	r= −.126 β= .124 t=1.455 p=.148	r= −.066 β= .034 t=.378 p=.706	r= −.106 β= .030 t= ,329 p=.743	r= .014 β=.171 t= 2.050 p=.040	r= 0.012 β= 0.154 t= 1.89 p= 0.060	r=−.397 β=−.513 t=−3.335 p=.002	r=−.501 β=−.561 t=−3.778 p=.001	r=−.510 β=−.602 t=−3.827 p=.001
Mental flexibility/ Working memory	r= −.179 β= −.212 t= −2.523 p=.013	r=−.219 β= −.273 t= −3.104 p=.002	r=−.169 β= −.217 t= −2.477 p=.014	r= .010 β=0.121 t= 1.75 p=.081	r= 0.006 β=0,090 t=1.34 p=.183			
Verbal learning and memory	r= −.018 β=.019 t=.208 p=.836	r= .018 β=.004 t= .043 p=.965	r= .040 β=.035 t=.397 p=.692	r= ,001 β=.033 t=.450 p=.653	r= .001 β= .000 t=.000 p=.996	r=−.333 β=−.311 t=−2.141 p=.041		
Executive function	NA	NA	NA	r=.001 β=.020 t=.340 p=.736	r= .001 β=.007 t=.120 p=.903	r=.306 β=.415 t=2.478 p=.020	r=.384 β=.411 t=2.884 p=.007	r=.227 β=.284 t=1.812 p=.080

NA=not available