Supplement_F_PICO_4_Non-adherence on outcome

PICO 4: Effect of non-adherence on outcome.

Assuming non-adherence has a negative impact on treatment outcome, the question remains what are the effects of adherence interventions on the clinical outcome?

All interventions included in the selected systematic reviews were reviewed. The primary outcome in the studies were adherence. Only studies that measured clinical outcomes (disease activity [DAS-28, CDAI], data on patient's perspective [QoL, function, and fatigue]) in addition to adherence were included.

Summary

In total, 5 reviews , including 15 RCT studies, describing interventions, which had a significantly positive effect on adherent behaviour were included in this analysis (9 studies[1-9] on medication adherence; 6 on non-pharmacological/exercise adherence[10-15]). Studies were excluded, if they did not reach significance[16-23], if the intervention only focused on rheumatologists[24], focused on health literacy only[25], or the study was not a RCT[26-28], intervetions to improve adherence was not an object of the study[29-44], or if the study did not focus on RMDs (ulcerative colitis[45-49], inflammatory bowel diseases[50]).

Medication adherence

Patients in the 9 included studies regarding medication adherence, patients were diagnosed with rheumatoid arthritis (RA)[2-5, 8], psoriasis[1], systemic lupus erythematosus (SLE)[6, 9], juvenile rheumatoid arthritis (JRA)[7]. Chages in clinical outcomes due to a change in adherence were seen in:

1) Decrease in disease severity[1]/activity[9], pain[1, 3, 4], PGA[1, 3, 4], functional disability[1, 3, 4, 8], DAS-28[3, 4], fatique[8].
2) Increase in quality of life[1, 3, 4], knowledge[6], active coping with stress[8].
3) Decrease of helplessness[4], medicine related problems[5], depression[8].
4) Increase in quality of patient–physician communication[1].

Exercise adherence

In the 6 included studies dealing with exercise adherence, patients were diagnosed with osteoarthritis[10, 12, 15], low back pain[11] , and RA[13, 14]. The group that was significantly more adherent, had also significant improvements in:

physical activity[10, 12-14], functioning[11, 15], quality of life[11], proxy efficacy (refers to patients' confidence in their therapists' ability to function effectively on their behalf)[11], working alliance[11], treatment expectancy[11], and a decrease in pain[15] and weight[10]

Table 1. Individual studies exploring effective communication and SDM components of interventions proven effective.

Study, Design, med/non-pharma	Review	Dig., IG, CG	Intervention	Outcome measures	Results
Studies with significant effects on medication adherence					
Balato, Megna [1]; Pilot RCT; medication	Depont, Berenbaum [51]	Psoriasis IG n=20 CG n=20	IG: Daily text messages (TM), providing reminders and educational tools CG: not clear	At the beginning and endof the study the following assessments were performed: Psoriasis Area SeverityIndex (PASI), Self-Administered Psoriasis Area Severity Index (SAPASI), body sur-face area (BSA), Physician Global Assessment (PGA), Dermatology Life QualityIndex (DLQI), evaluation of patient–physician relationship and adherence to ther-apy.	intervention group reported a significantly better improvement of disease severity as well as quality of life, showing lower values of PASI, SAPASI, BSA, PGA and DLQI; optimization of patient–physician communication compared to the control group (P<.05) (values are not reported, can only be estimated from the figures). Adherence to therapy improved astatistically significant way (3.86 to 6.46 days per week P<.001) whereas it remained stable in the control group. TM led to an optimization of patient–physician communication.
Hill, Bird [2]; RCT; medication	Depont, Berenbaum [51]	RA IG n=51 CG n=49	IG: patient education programme: information about the types of drugs used for RA, the disease process, physical exercise, joint protection, pain control, and coping strategies. Written information, including a DPA drug information leaflet developed specially for the study, was provided as back up. CG: same DPA drug information leaflet	primary measure of adherence was by pharmacological marker (dosage of DPA) (The ratio of phenobarbitone level in the blood to prescribed dose (LDR) was calculated for each patient at each study visit: (phenobarbitone concentration (mg/l))/(daily phenobarbitone dose (mg/kg body weight)).	pharmacological marker showed the EG to be significantly more adherent on more occasions than the CG (p<0.05). Patterns of adherence over time showed that at 12 weeks 86% (38/44) of those in the EG compared with 64% (29/45) of the CG remained adherent (p=0.01). These trends continued and by the end of the study 85% (29/34) of the EG compared with 55% (23/42) of the CG were taking their DPA as prescribed.
El Miedany, El Gaafary [3]; Pilot RCT; medication	Depont, Berenbaum [51]	Early RA IG n=55 CG n=56	IG: visual feedback facility (visualization of computer charts showing the disease progression) CG: Usual care	Primary outcome: change in the patients' adherence to their medications, disease activity score (DAS-28), and PROMs domains: pain score, patient global assessment, functional disability, and quality of life.	Adherence: IG 47/54 (87%) patients in were adherent to their drug therapy, whereas 23/54 (43%) in CG to their drug therapy (P < 0.01). Pain (IG 4.48 (1.4) vs CG 3.39 (1.1), p <0.001), PGA (IG 4.22 (1.2), CG 3.41 (1.1), p <0.001), functional disability (IG 1.75 (0.3), CG 1.21 (0.3), p <0.001), QoL (IG 1.77 (0.2), CG 1.30 (0.2), p <0.001), DAS28 (IG 1.79 (0.4), CG 1.23 (0.3), p <0.001)
El Miedany, El Gaafary [4]; RCT;	Depont, Berenbaum [51]	RA IG n=74 CG n=73	IG: Joint-fitness programme combined with discussion/review of PROMs and patient education; The programme includes 4 main com-ponents: a) educational – joint-learn, b) behavioural – joint-change, c) informa-tion – joint act and d) joint-cise (joint-exercise).	At 3, 12 and 18 months: The primary outcome was the change in the patients' adherence to their medications, disease activity score (DAS-28) and PROMs (pain score, patient global assessment, functional	significant reduction DAS-28 score, as well as improvement of the patients' adherence to therapy (p<0.01), improvement of disease activity was associated with improvement in functional disability and quality of life scores. At 18 months: Pain (IG 4.49 (1.3) vs CG 3.38 (1.1), p <0.001), PGA (IG 4.25 (1.1), CG 3.43 (1.2), p

Study, Design, med/non-pharma	Review	Dig., IG, CG	Intervention	Outcome measures	Results
medication			CG: usual care	disability, quality of life and self-help-lessness).	<0.001), functional disability (IG 1.76 (0.2), CG 1.22 (0.4), p <0.001), QoL (IG 1.76 (0.2), CG 1.31 (0.2), p <0.001), Helplessness (IG 4.7 (0.4), CG 3.1 (0.5), p <0.001), DAS28 (IG 1.79 (0.3), CG 1.21 (0.2), p <0.001)
Clifford, Barber [5]; RCT; medication	Galo, Mehat [52]	RA IG n=261 CG n=239	IG: telephone-based, patient-tailored pharmacy advisory service delivered by community pharmacists to elderly patients which included RA. The pharmacist gave information, advice or reassurance in response to the patients' expressed needs. CG: usual care	Primary Outcome: Incidence of non-adherence Secondary outcome: problems with the new medicine, beliefs about the new medicine, safety and usefulness of the interventions.	non-adherence significantly lower in the intervention group (9% vs. 16%, P = 0.032), patients reporting medicine related problems was lower (23% vs. 34%, P = 0.021), more positive beliefs about their new medicine, as shown by their higher score on the "necessity-concerns differential" (5.0 vs. 3.5, P = 0.007).
Ganachari and Almas [6]; RCT; medication	Galo, Mehat [52]	SLE IG n=21 CG n=20	IG: education regarding SLE and its management by clinical pharmacist: including lifestyle modifications, via the distribution of patient information CG: usual care	Knowledge Assessment Questionnaire, Medication Adherence Questionnaire	significant improvement in the medication knowledge (Baseline / follow up: IC 15 ± 1.855 vs. CG 7 ± 1.744 < 0.001 and baseline/second follow up IC 16 ± 1.576 vs. CG 7 ± 1.945 < 0.001); mean medication adherence score increase in the IC from 3.0 to 5.8 at post-counselling and was also a significant better when compared with the CG (4.6).
Rapoff, Belmont [7]; RCT; medication	Galo, Mehat [52]	Juvenile Rheumatoid Arthritis IG n=19 CG n=15	IG: educational and behavioral strategies for enhancing adherence: 10-min audiovisual program and received abooklet which described adherence-enhancement strategies: cueing(e.g., pairing medication taking with an established behavior such as brushing teeth), monitoring (e.g., using a calendar to trackmedication taking), positive reinforcement (e.g., praising and rewarding with tokens that are exchanged for special privileges), and discipline (e.g.,using time-out for defiant refusals to take medications). Nurse reviewd and rehearsed stategies, gave answers CG: received a general educational on JRA	Adherence: Medication Event Mon-itoring System (MEMS), Disease activity and functional status (standard clinical indices, number of active joints, minutes of morning stiffness, and global disease activity rating), Childhood Health Assessment Questionnaire (CHAQ),	significant differences in adherence as measured by Medication Event Monitoring Systems between the intervention and control groups (77.7±21.5 vs 56.9±33.0, p=0.02). groups did not differ significantly in disease activity or functional limitations
Evers, Kraaimaat [8];	Depont, Beren	Early RA IG n=32 CG n=32	IG: cognitive-behavioural therapy (CBT): consisted of individual treatment with two out of the four treatment modules:	Disease activity: Disease Activity Score (DAS); Functional disability: Mobility and Self-care scales of	disease activity ($F(2,55)=2.03$, $P<0.14$); (functional disability, pain, fatigue) revealed a significant time×condition effect, Wilks' $\lambda=0.73$,

Study, Design, med/non-pharma	Review	Dig., IG, CG	Intervention	Outcome measures	Results
RCT; medication	baum [51]		pain and functional disability, fatigue, negative mood and social relationships. CG: usual care	the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL); ; Pain: IRGL Pain scale (six items); Fatigue: Checklist Individual Strength (CIS); Psychological functioning: IRGL Anxiety and Negative Mood scales; Social functioning: IRGL social functioning scales; Illness cognitions: Illness Cognition Questionnaire; Coping with stress: Utrechtse Coping Lijst (UCL); Coping with pain: Pain Coping Inventory (PCI); Compliance with RA medication: 3-point scale by a single item, inquiring about the frequency of failing to take the prescribed RA medication during the previous month (1=once a week or more, 2=less than once in a week, 3=never).	F(6,51)=3.16, P<0.05. Univariate tests: fatigue (F(2,55)=4.17, P<0.05). fatigue significantly decreased in the CBT condition at post-treatment and follow-up assessment (t=3.09, P<0.01 and t=3.14, P<0.01, respectively), but not in the control condition (t=1.18, P=0.25 and t=−1.44, P=0.16, respectively). Univariate condition×time interactions were not significant for functional disability and pain (F(2,55)=1.82, P=0.17 and F(2,55)=0.27, P=0.77, respectively); (depression, negative mood, anxiety), Wilks' λ=0.73, F(6,51)=3.20, P<0.05. Univariate tests showed a significant effect for depression (F(2,55)=5.34, P<0.01), demonstrating that depression significantly decreased in the CBT condition at post-treatment and follow-up assessment (t=3.02, P<0.01 and t=3.10, P<0.01, respectively), but not in the control condition (t=−0.57, P=0.58 and t=−1.23, P=0.23, respectively). No significant for negative mood and anxiety (F(2,55)=1.30, P=0.28 and F(2,55)=0.67, P=0.52, respectively). Significant for active coping with stress (F(2,55)=3.85, P<0.05). the CBT condition used significantly more active coping strategies when dealing with stress at post-treatment (t=−2.88, P<0.01), but not at follow-up assessment (t=−1.44, P=0.16), while active coping with stress did not significantly change in the control condition at both assessment points (t=0.80, P=0.43 and t=0.22, P=0.83, respectively).
Ting, Kudalkar [9]	Galo, Mehat [52]	childhood-onset SLE IG n=19 CG n=22	IG: cellular text messaging reminders (CTMR) to remind taking medication and to remind for CG: usual care	Systemic Lupus International Collaborating Clinics/American College of RheumatologyDamage Index (SDI), the Systemic Lupus Erythematosus Disease ActivityIndex (SLEDAI), and the physician assessment of disease activity (by visu-al analog scale; range 0–10, 0 = inactive disease, 10 = very active disease).The number of emergency room (ER)	At baseline, 32% of patients were sufficiently adherent to HCQ, and 81% to clinic visits.Visit adherence improved significantly by > 80% among those who were nonadherent to clinic visitsat the baseline CTMR (p = 0.01). CTMR did not influence adherence to HCQ over time. As expected, those patients who were seen more fre-quently over time generally had more no-shows, had worse SLEDAI scores, had more ER visits and more frequent hospital admissions, and were treated with a higher

Study, Design, med/non-pharma	Review	Dig., IG, CG	Intervention	Outcome measures	Results
				visits and the number of hospital admissions were monitored among patients participating in clinic visit adherence.	number of medications. In contrast, patients who were adherent to visits had overall lower SLEDAI scores across all time periods. Among patients who were no adherent, rescheduling (cancellation) rates also increased greatly during the CTMR intervention (effect size, d = 0.78).
Studies with significant effects on non-pharmacological intervention adherence					
Ravaud, Flipo [10]; RCT; Non-pharma	Ezzat, MacPherson [53]	OA/knee, IG n=154 CG n=182	IG: Standardised consultation during three goal oriented visits: education on osteoarthritis and treatment management, information on physical exercises, information on weight loss. CG: usual care	Change in (1) body weight; (2) time spent on physical exercises (Baecke index)	4 months: 1) decrease in weight (mean −1.11 (SD 2.49) kg v −0.37 (2.39) kg; P=0.007) 2) physical activity score (mean 0.20 (0.65) v 0.04 (0.78); P=0.013)
Vong, Cheing [11]; RCT; Non-pharma	Nicolson, Bennell [54]	Low Back Pain IG n=38 CG n=38	IG: motivational enhancement treatment (MET) including supporting appropriate behaviour change and increasing self-efficacy PLUS PT CG: conventional physical therapy (PT)	Motivational-enhancing factors (PRES and PSEQ), pain intensity (VAS), physical functions (trunk motion and RMDQ), and exercise compliance (exercise log book).	The MET-plus-PT group produced significantly greater improvements than the PT group in 3 motivation-enhancing factors; proxy efficacy (P<.001), working alliance (P<.001), and treatment expectancy (P=.011). Furthermore, they performed significantly better in lifting capacity (P=.015), 36-Item Short Form Health Survey General Health subscale (P=.015), and exercise compliance (P=.002) than the PT group. A trend of a greater decrease in visual analog scale and Roland-Morris Disability Questionnaire scores also was found in the MET-plus-PT group than the PT group. Adherence: The MET-plus-PT group performed home exercises 2 times more frequently than the PT group in session 10 (MET-plus-PT, 13.9±8.2 vs PT, 6.2±3.6sessions/wk) and 1-month follow-up (MET-plus-PT, 12.9±7.2 vs PT, 5.8±4.1sessions/wk).
Halbert, Crotty [12]; RCT; Non-pharma	Ezzat, MacPherson [53]	OA IG n=37 CG n=32	IG: individualized physical activity advice CG: received a pamphlet on good nutrition	Intention to exercise was: self-reported questionnaire Physical activity outcomes included frequency of walking per week, minutes of walking per session, frequency of vigorous exercise per week, and minutes of vigorous exercise per session. Intention to exercise was measured using a stages-of-	Reported increases in frequency and time of walking and vigorous exercise (all P<0.001), with no change to OA symptom scores (pain and stiffness), and a small decline in physical functioning was reported at 12 months follow up in the control group only (P=0.027). At the 12-month follow up more intervention participants than control participants (P=0.013) reported a greater intention to exercise. (More numbers are

Study, Design, med/non-pharma	Review	Dig., IG, CG	Intervention	Outcome measures	Results
				change approach (14)Self-reported symptoms of OA were assessed with the use of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)(15). Clinical recordings included resting heart rate, seated blood pressure, height, and mass, and 5 ml of blood was taken for a blood lipid profile. An examination of both knees by one of the investigators (JH) was conducted on all patients in the intervention group to determine the absence or presence of warmth, crepitus, joint margin tenderness, and swelling.	not reported, can be only estimated from the graphs).
Brus, Van De Laar [13] RCT; medication	Depont, Berenbaum [51]	RA IG n=25 CG n=30	IC: education programme focused on compliance with sulphasalazine therapy, physical exercises, endurance activities (walking, swimming, and bicycling), advice on energy conservation, and joint protection, training was given in proper execution of physical exercises. Patients were encouraged to plan their treatment regimens. Their intentions were discussed and help was given in recasting unrealistic ones. Patients made contracts with themselves regarding their intentions. Feedback on the eventual implementation of therapeutic advice was included in each meeting.	physical exercise and with endurance activity regimens (walking, swimming, bicycling) were measured by questionnaire; patients were asked how many times a week and how many minutes average each time they performed these activities. Time spent on endurance activities were added.	Only at three months the increment of time spent on physical exercises was significantly greater in the experimental group ($p<0.05$) (table 2). During the observational period the time spent on endurance exercise did not differ significantly between groups (table 2)
Pisters, Veenhof [14]	Ezzat, MacPherson [53]	OA/hip, knee	IG: individually tailored graded exercise program to teach the patient that it is safe to move while increasing the level of activity. CG: usual care	Exercise adherence was measured using a questionnaire and physical activity was measured using the SQUASH questionnaire at baseline, 13, and 65 weeks.	Adherence to recommended exercises was significantly higher in the experimental group than in the control group at 13 weeks (OR 4.3, 95% CI 2.1 to 9.0) and at 65 weeks (OR 3.0, 95% CI 1.5 to 6.0). Significantly more of the experimental than the control group met the recommendations for physical activity at 13 weeks (OR 5.3, 95% CI 1.9 to 14.8) and at 65 weeks (OR 2.9, 95% CI 1.2 to 6.7).

Study, Design, med/non-pharma	Review	Dig., IG, CG	Intervention	Outcome measures	Results
Tüzün, Cifcili [15]	Nicolson, Bennell [54]	Knee OA	IG: Photos displaying these exercises were taken, and explanatory information was written next to the relevant photo using large fonts. CG: usual care	The compliance of the participant: logs and weekly follow-up via phone call performed by a blind investigator. Effectiveness of the therapy: (1) WOMAC score (2) Quadriceps measurements 15 cm proximal to the tuberositas tibiae	These analyses revealed that 100% of the participants in the IG were compliant with all assessments, and 80% of the participants in the SCG were compliant in the first week, and the rate of compliance decreased to 70% at Week 5 and to 55% at Week 10 (p=0.0001). The CEP in the SCG was 80% at Week 1 (55.0 – 100.0), 70% at Week 5 (55.0 – 93.75), and 55% at Week 10 (17.5 – 70) (p=0.001), and the most significant decrease in the CEP occurred between Weeks 5 and 10 (p=0.0001). The median WOMAC values of the participants in the IG and SCG were 43.5 (25.75 – 50.25) and 36.0 (23.5 - 42.25) (p=0.276), and the final WOMAC values decreased by 9.5 (5.0 - 18.0) and 27.0 (15.25 - 39.0), respectively. The analysis of WOMAC measurements revealed that the decrease was significant in both groups, yielding a p value of 0.037 in the SCG and 0.0001 in the IG. The comparison of the decrease in WOMAC values between the groups: yielded a value of p=0.0001. The evaluation of the median BMI values between the initial and final assessment revealed a significant decrease (p=0.005). When the participants were evaluated according to their randomization groups, the decrease was significant in SCG (p=0.012) and insignificant in the IG (p=0.179). Furthermore, there was no significant difference between the groups in terms of the measurement of the quadriceps circumference.

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