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Review
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A COLLABORATIVE CARE MODEL BETWEEN GENERAL PRACTITIONERS AND CLINICAL PHARMACISTS IN A COMMUNITY HEALTH CENTRE SETTING IN DEPRESSION TREATMENT

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SUMMARY

Background: *A collaborative care model between clinical pharmacists (CP) and general practitioners (GPs) for treating patients with treatment-resistant depression (TRD) and major depressive disorder (MDD) has not been described yet in the medical literature in Central Europe. Therefore, the main aim of this paper was compared standard of care and collaborative care model including clinical pharmacist in a systematic review form.*

Subjects and method: *A systematic search in Pubmed/Medline using the terms pharmacist, depression, and primary care in Medline through to September 2016 was conducted to identify randomized controlled clinical trials (RCTs). The patient's data for the case report was obtained from the medical records.*

Results: *23 RCTs were found. In total 3 RCTs were included in this systematic review. Efficacy in reducing depressive symptoms in collaborative care model compared to the standard of care (without clinical pharmacist) were shown in all RCTs. A collaborative care model also showed positive treatment outcomes in case report.*

Conclusion: *This systematic review shows positive treatment outcomes in patients included in collaborative care model compared to current standard of care. This positive case report shows evidence for the effectiveness of a collaborative care model with a CP in a primary care setting. CPs can assist GPs in choosing the appropriate pharmacotherapy.*

Key words: *clinical pharmacy - general practitioner - systematic reviews - collaborative care model - antidepressant combination*

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INTRODUCTION

Medical errors (a preventable adverse effect of care) and polypharmacy (the simultaneous use of multiple drugs), are associated with compliance errors and adverse drug reactions and are a high burden for patients and health service providers. A 2016 study found that medical errors are the third leading cause of death in the United States, after heart disease and cancer. Researchers looked at studies that analysed the medical death rate data from 2000 to 2008 and extrapolated that over 250.000 deaths per year stemmed from medical errors, which is 9.5% of all deaths annually in the US (Frellick & Marcia 2016). One of the most effective systems that prevent medical errors is a collaborative care model, where clinical pharmacists are included in the patients' pharmacotherapy. Pharmacist reviews of medication orders in intensive care units (ICUs) have been shown to prevent errors, pharmacist consultation has reduced drug costs, and having a pharmacist as a full member in the patient care team was associated with a substantially lower rate of adverse drug effects caused by prescribing errors (Leape et al. 1999). Although this system has been well described in the U.S. and UK, there are almost no data on such collaboration care models in Central and Eastern Europe, primarily because pharmacists and physicians traditionally have had rigid and separate roles (pharmacists as dispensers, physicians as prescribers), so direct patient care and medical errors were rarely discussed. Because of a large increase in drug consumption in the last decade in Slovenia, The Health Insurance Institute of Slovenia (Slovene: Zavod za zdravstveno zavarovanje Slovenije, ZZZS) was interested in avoiding major adverse effects of polypharmacy in clinical practice. For this purpose, ZZZS had financed a pilot trial titled Pharmacist Consultant, in which a clinical pharmacy specialist was enrolled into each medical primary team. Each team consisted of all general practitioners (GPs) at a community health centre and one pharmacist consultant (PC), who were either clinical pharmacy specialists or pursing education to become that. GPs could send patients to the PC, who communicated with patients and prepared a pharmacotherapy review. The review was sent back to the GPs. The patient then visited the GPs and then he/she decided to accept or reject the PCs recommendations on pharmacotherapy. The pharmacotherapy review included the following important aspects: drug-drug interactions, possible adverse events, existing drug indications, possible inappropriate medication in the elderly and final recommendations depending on the patient's outcomes. This pilot project lasted 3 years and had positive results. The pilot trial was conducted in all 4 community health centres in the

region of Pomurje in Eastern Slovenia. By 2018, all community health centres will have their own PCs, funded by the ZZZS (Premuš Marušič & Štuhec 2016). Almost all medications and medical services in Slovenia in primary care are paid by the ZZZS and once a program is funded by the ZZZS, the funding is likely to be continued. The described collaborative care model offers a new pharmacotherapy service, which has not been established in any country in Central and Eastern Europe. The main aim of this paper is to present a successful application of a collaborative care model in a primary care setting in depression treatment and to provide systematic review about this service. This paper also aims to promote more Central and Eastern European countries to implement this collaboration care model.

SUBJECTS AND METHODS

Search Strategy

Prior to study, a PubMed (last search: 1 September 2016, PubMed/MEDLINE) search was conducted using the terms "pharmacist" AND "primary care" AND "depression" to identify randomized controlled trials and case reports in order to evaluate the possible effects of this cooperation in these settings. We did not apply restrictions regarding date, language, or publishing status but excluded conference abstracts that were not published as journal articles. We searched reference lists in relevant systematic reviews with meta-analyses. We did not contact study authors to identify any additional studies. Also, the references of selected full text articles were searched. Details of systematic review have also been presented in the flowchart form.

Included study and data extraction and analysis

Only double blind randomized controlled trials (RCTs) were enrolled. Studies where methodology was unclear (e.g. treatment outcomes were not defined, standard deviations not included etc.) were excluded from this review. For inclusion in the systematic review, studies had to meet predefined PICOS requirements (Population or disease, Interventions or exposure, Comparator, Outcomes, Study design)) (Shamseer et al. 2015). Only RCTs that measured outcomes of depression symptoms were included in the systematic review. We did not set the minimal duration of the studies and age of included participants.

Both reviewers independently searched for appropriate RCTs to predefined selection criteria. The data of interest were as follows: authors, year of publication, type of pharmacist intervention, study outcomes, number of randomized subjects in both groups, study duration and type of scales used. We collected mean changes (MD) from baseline to end point with their standard deviations (SD) in both groups for values where applicable.

RESULTS

Case report results

A 62-year-old Caucasian Slovenian female was sent to a PC in a primary care setting in Ljutomer in 2013 because of major depressive disorder (MDD) pharmacotherapy, connected to chronic neuropathic pain. She was diagnosed with major depressive disorder (F32) and chronic neuropathic pain (F60.2). Her problems started at 45, and by 2016 she suffered many relapses of MDD. In the last few years she often used benzodiazepines to treat insomnia. She denied drinking alcohol, using herbal products, and smoking, did not report any past drug allergies, and had very good drug adherence. Her platelet count, liver enzyme levels, thyroid function, and liver function were within normal ranges. Before being sent to a PC she was being treated with the following medications: quetiapine 25 mg daily at bedtime, bupropion 150 mg in XL formulation daily, tramadol/paracetamol 37.5/325 mg once daily, agomelatine 25 mg daily at bedtime, omeprazole 20 mg daily, and some medications as needed (zolpidem 5 mg, paracetamol 500 mg, trospium chloride 5 mg, meloxicam 10 mg). In the PC's review, the PC first checked the patient's dispensing history and confirmed good adherence to medication. Next, the patient's knowledge about her pharmacotherapy was checked (names and indications) and was found to be very good. Possible drug-drug interactions were checked with Lexi Comp® Online 19.0. and were found to not be important in this patient. Because of severe insomnia, which persisted despite the agomelatine treatment, the PC suggested adding trazodone 45 minutes before bedtime (titrated up to 150 mg daily in 7 days) to the treatment and the discontinuation of agomelatine and quetiapine. The PC also suggested adding duloxetine titrated to 120 mg daily and the discontinuation of tramadol/paracetamol. Esomeprazole was also suggested instead of omeprazole, because patients paid extra for omeprazole. The patient's GP examined the PC's report and accepted all the recommendations and then measured the MDD status with the 17-item Hamilton Rating Scale for Depression (HAM-D17) and neuropathic pain statues with the Visual Analog Scale for Pain (VAS). After 4 weeks of treatment, the patient's HAM-D17 score dropped from 28 to under 7 (full remission was achieved). The VAS score also decreased by 50% and the GP's subjective assessment of the patient's health also improved and no adverse medication withdrawal events were observed. The cognitive and psychiatric symptoms did not worsen when medication was discontinued and adverse medication withdrawal events were not observed. After almost 3 years the patient still uses this pharmacotherapy and MDD remission has been maintained. The 17-item Hamilton Rating Scale for Depression (HAM-D17) has been used to assess the response and remission to therapy in this clinical case (McIntyre et al. 2002).

Table 1. Summary of study characteristics

Author, Year	Study size (N) in control/intervention group	Study outcomes	Rating scale used	Outcome measured	Type of clinical pharmacist intervention	Duration (weeks)
Finley 2003	Control (50/125) Intervetion (75/125)	a) 18.3±5.8 (baseline) a) 18.7±5.8 (baseline) b) -8.9±8.3 (6 months) b) -6.6±7.3 (6 months) 1) 57 patients (76%) in the intervention group were compliant with the early phase of treatment (vs 30 [60%] in the control group, OR 2.11, 95% confidence interval [CI] 0.97–4.58, p=0.057) 2) 50 patients (67%) completed the continuation phase (vs 24 [48%] in the control group, OR 2.17, CI 1.04–4.51, p=0.038)	BIDS = Brief Inventory for Depressive Symptoms NA	Depressive Symptoms Compliance	Under an institutional protocol approved by the medical center's Pharmacy and Therapeutics Committee, the care managers (or clinical pharmacists) were permitted to titrate antidepressant drugs in a manner consistent with the clinical practice guidelines and current Recommended prescribing practices. The pharmacists were also allowed to prescribe ancillary drugs (e.g., trazodone for sleep), but if a change in antidepressant drugs was indicated, approval from the primary care provider was required	24
Boudreau 2002	Control (33/74) Intervetion (41/74)	(21 patients, 53%) (Usual care) (9 patients, 28%) (Intervention group-Enhanced care) p=0.04 1.83 ± 0.10 (Usual care) 1.75 ± 0.10 (Intervention group-Enhanced group), p=0.55	SCID = Structured Clinical Interview for DSM-IV Hopkins Symptom Checklist (SCL-20)	Depressive Symptoms Depressive Symptoms	Telephone interview and pharmacists and study psychiatrist reviewed individual cases or had informal discussion sessions regarding treatment or counseling	48
Adler 2004	Control (265/533) Intervetion (268/533)	Six-month antidepressant (AD) use rates for intervention patients exceeded controls (57.5% vs. 46.2%, P<0.03) Patients taking ADs had better modified Beck Depression Inventory (mBDI) outcomes than patients not taking ADs, (6.3 points change, vs. 2.8, P<0.01) but the outcome differences between intervention and control patients were not statistically significant (17.7 BDI points vs. 19.4 BDI points, P < 0.16)	NA Beck Depression Inventory (mBDI	Antidepressant (AD) use rates Depressive Symptoms	Consultation in person and by telephone was performed by a clinical pharmacist who assisted the primary care practitioner (PCP) and patient in medication choice, dose, and regimen, in accordance with AHCPR depression guidelines	24

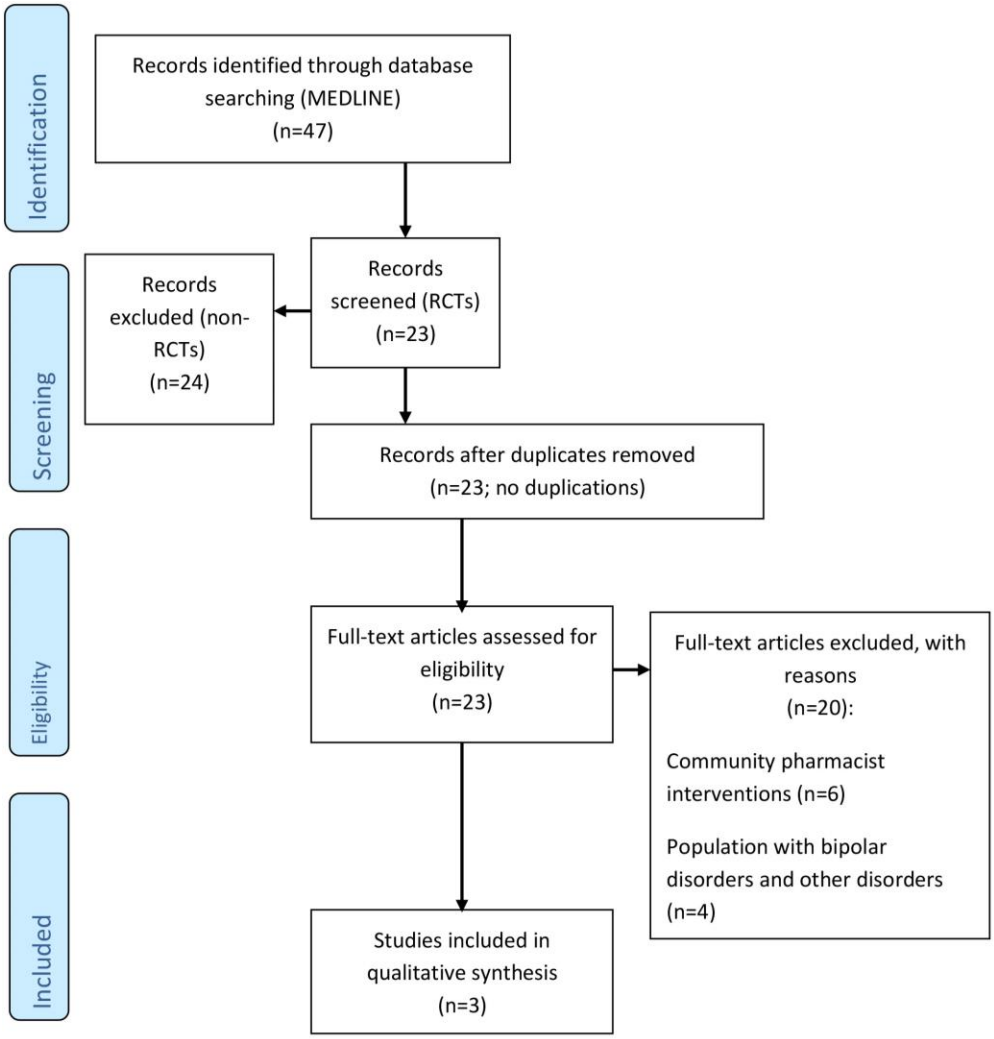

Figure 1. A flow chart of selection of the searched studies

Systematic Review Results

23 RCTs were found in Medline, although only 3 RCTs were appropriate according to the eligibility assessment. 3 RCTs were included in the systematic review (all results are summarized in the Table 1) (Finley et al. 2004, Boudreau et al. 2002, Adler et al. 2004).

Most of the RCTs were not included because they included interventions done by a community pharmacist (not clinical pharmacist within this type of care). Other RCTs were excluded because of methodology. Details of systematic review have also been presented in the Figure. 1.

DISCUSSION

There are no findings on PubMed or Medline on the use of this collaborative care model in Central Europe. Firstly, TRD was also treated appropriately with a combination of trazodone, duloxetine and bupropion in this case. This case report demonstrates the effectiveness of the collaborative care model in Slovenia in treating patients with MDD, because full remission was observed in this patient.

Secondly, the most important aspect of this article is that this novel approach in psychiatry can lead to better clinical outcomes (collaborative care vs. standard of care), which was also supported by 3 RCTs included in this systematic review (Finley et al. 2004, Boudreau et al. 2002, Adler et al. 2004). In RCTs published by Finley et al. included in our systematic review, comparing the outcomes of subjects treated under this collaborative care model (75 patients, intervention group) with subjects receiving usual care (50 patients, control group). After 6 months, the intervention group demonstrated a significantly higher drug adherence rate than the control group (67% vs 48%, odds ratio 2.17, 95% confidence interval 1.04-4.51, P =0.038). Patient satisfaction was significantly greater in the intervention than in the control group, and provider satisfaction surveys revealed high approval rates as well. Clinical improvement was noted in both groups, but the difference was not significant (Finley et al. 2003). In study published by Adler et al., patients taking

antidepressants (ADs) had better modified Beck Depression Inventory (mBDI) outcomes than patients not taking ADs, (6.3 points change, vs. 2.8, P<0.01) but the outcome differences between intervention and control patients were not statistically significant (17.7 BDI points vs. 19.4 BDI points, P<0.16). This RCTs consultation was performed by a clinical pharmacist in person and by telephone without a patient visit at each appointment, which is an important limitation (Adler et al. 2004). Similar limitations and results have been observed in the third included RCTs published by Boudreau et al. 2002.

In addition, another prospective, nonrandomized, proof-of-concept investigation was conducted from July 2006 to December 2007. Of the 151 beneficiaries referred to the program, 130 (82%) remained under pharmacist care for a minimum of 1 year and were included in the aggregate analysis. Statistically significant improvements were observed in the Patient Health Questionnaire (PHQ-9) scores from baseline to endpoint (11.5 ± 6.6 to 5.3 ± 4.7 [mean ± SD], $P < 0.0001$). The clinical response rate was 68% with a 56% remission rate. An economic subgroup analysis (n=48) revealed that annual medical costs decreased from an average of $6.351 per enrolee to $5.876, which was lower than the projected value ($7,195). Total health care costs to employers increased from $7.935 per enrolee to $8.040, which was lower than the projected value ($9.023). Total health care costs per patient per year were reduced compared with projected costs without the program (Finley et al. 2011). Because of these positive results, this service was adopted in parts of the U.S., especially California, where this service is paid by health insurance companies. Pharmacists were given a new role, moving from dispensers to providers, which is a trend seen in the U.S. and also in Slovenia recently. There are many published case reports in Slovenian psychiatric hospitals that this type of collaboration is beneficial for patients with mood disorders, although this is the first case report on a primary care setting in this part of Europe (Stuhec 2013, Štuhec 2013, 2015). Despite of the positive results from the U.S., such a model has not been described in the literature in Central Europe. Slovenian general medicine students now learn about this collaborative care model to better understand the importance of cooperation in clinical practice. This practice has not been seen in any other country in Central Europe. In addition, Kessler, et al. reported that MDD treatment was adequate in only 41.9% (95% CI, 35.9-47.9) of cases, resulting in 21.7% (95% CI, 18.1-25.2) of 12-month MDD being adequately treated (N=9090), which means that a collaborative care model between general practitioners and clinical pharmacists in a community health centre setting could be an important step towards higher number of adequately treated patients with MDD (Kessler et al. 2003).

This study has also many important limitations. First important limitation is only single case report, which is difficult to replicate. Second limitation is a study design and inclusion criteria, which can exclude some important papers (especially papers in naturalistic settings, which have no RCTs design). Third important limitation is a study origin, because all 3 included RCTs have been conducted in U.S., where collaborative care including clinical pharmacist is well-known standard of care. The last important limitation is a lack of systematic risk of bias (e.g. Cochrane RoB 1.0 tool), although only 3 RCTs were included and their important bias has been already discussed.

CONCLUSION

The collaborative care model was shown to be efficient in our case report as well as other included studies. We hope this report will support clinicians and pharmacists in the treatment of TRD and serve as the impetus for further published case reports and clinical studies on collaborative care models. Finally, and perhaps most importantly, this paper on this topic is the first of its kind in the PubMed database and could serve as a stepping stone for future research of this type of collaboration in this part of Europe in primary care settings (e.g. Austria, Hungary, Croatia).

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Conflict of interest:

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All authors contributed to writing of this paper equally.

References

1. *Adler DA, Bungay KM, Wilson IB, Pei Y, Supran S, Peckham E, Cynn DJ, Rogers WH: The impact of a pharmacist intervention on 6-month outcomes in depressed primary care patients. Gen Hosp Psychiatry 2004; 26:199-209*
2. *Boudreau DM, Capoccia KL, Sullivan SD, Blough DK, Ellsworth AJ, Clark DL, Katon WJ, Walker EA, Stevens NG: Collaborative care model to improve*

outcomes in major depression. Ann Pharmacother 2002; 36:585-591

3. *Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ: What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. J Affect Disord 2009; 116: 4-11*
4. *Finley PR, Rens HR, Pont JT, Gess SL, Louie C, Bull SA et al: Impact of a collaborative care model on depression in a primary care setting: a randomized controlled trial. Pharmacotherapy 2003; 23:1175-85*
5. *Finley PR, Bluml BM, Bunting BA, Kiser SN: Clinical and economic outcomes of a pilot project examining pharmacist-focused collaborative care treatment for depression. J Am Pharm Assoc 2011; 51:40-9*
6. *Frellick, Marcia: "Medical Error Is Third Leading Cause of Death in US Marcia Frellick". Medscape. Retrieved 7 May 2016*
7. *Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR et al: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289:3095-105*
8. *Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI: Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 1999; 282:267-70*
9. *McIntyre R, Kennedy S, Bagby RM et al.: Assessing full remission. J Psychiatry Neurosci 2002; 27: 235-39*
10. *Premuš Marušič A, Štuhec M: The new roles of pharmacists in Slovenia : use of medication review and medication reconciliation in clinical practice. V: Jakševac Mikša, Maja (ur.). Ljekarništvo i farmaceutska industrija 2020.: XVIII. savjetovanje farmaceuta. Zagreb: Hrvatsko farmaceutsko društvo, 2016, str. 31-33.*
11. *Savarese M, Carnicelli M, Cardinali V, Mogavero MP, Federico F: Subjective hypnotic efficacy of Trazodone and Mirtazapine in patients with chronic insomnia: a retrospective, comparative study. Arch Ital Bio. 2015; 153:231-38*
12. *Shamseer L, Moher D, Clarke M et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 349: g7647*
13. *Stuhec M, Svab V, Malešič I: Clomethiazole-induced hepatotoxicity - a case report. Psychiatr Danub 2013; 25:182-4*
14. *Štuhec M: Agomelatine-induced hepatotoxicity. Wien Klin Wochenschr 2013; 125:225-26*
15. *Štuhec M: Excessive sweating induced by interaction between agomelatine and duloxetine hydrochloride: case report and review of the literature. 2015; 127:703-6*

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