Aspirin Use, Compliance, and Knowledge of Anticancer Effect in the Community

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ABSTRACT

Introduction: Millions of adults worldwide use low-dose aspirin for secondary prevention of heart disease. Results of randomized trials indicate that regular use of low-dose aspirin may reduce the risk of colorectal cancer by more than 20%, leading to speculation of its chemoprevention role for high-risk groups. Little is known, however, about the use of aspirin in our community.

Objective: To determine aspirin use and therapy compliance (never or rarely missing a dose) and to assess whether patients in our community are aware of its anticancer effect.

Methods: Observational study. Prospective data were collected during a 1-year period from patients in our general surgical clinic regarding aspirin use, comorbidities, adverse effects, and awareness of anticancer effect. Statistical analysis was performed.

Results: Among aspirin users (n = 137), the mean age was 65.8 years. Most (76.6%) received an 81-mg daily dose of aspirin. Compliance was 25.6% and was significantly associated with diabetes mellitus (p = 0.0028). Only 9.5% were aware of the medication's anticancer effect. Among nonusers (n = 383), the mean age was 53.3 years, a significant difference vs that of aspirin users (p < 0.001). Only 4.7% of nonusers knew of the anticancer effect. Nonusers were more likely to be women (p = 0.0005), younger than age 40 years (p < 0.0001), and have comorbidities or polypharmacy (p = 0.002). No significant difference was found between groups in anticoagulants use, nonsteroidal anti-inflammatory drug use, and smoking.

Conclusion: Knowledge of aspirin's anticancer effect is low. More research is required to understand why aspirin compliance is also low.

INTRODUCTION

Aspirin is used worldwide at low doses for secondary prevention of heart disease. There has been recent speculation regarding an additional role for aspirin: Chemoprevention of colorectal, breast, and other types of epithelial cancer.[1] The cyclooxygenase (COX) enzyme system, and its 2 isoenzymes, COX-1 and COX-2, play a key role in prostaglandin synthesis in both health and disease.[2,3] Excessive prostaglandin generation is thought to permit the progression of precursor epithelial lesions into cancers.[4] Abnormal expression of COX-2 is considered to be a key event in cancer promotion. It is an inducible isoenzyme, expressed after stimulation by growth factors and tumor promoters,[5-7] in turn generating uncontrolled prostaglandin release with all its negative sequelae.[8-10]

Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), inhibits the COX enzyme system at a low dose.[1] Findings of randomized controlled trials have recently indicated that regular administration of aspirin for 5 years can reduce the risk of colorectal cancer up to 27%.[11-13] Because millions of adults already use aspirin worldwide for the primary and secondary prevention of cardiovascular disease, considerable data already exist regarding its tolerability and side effect profile.[1,14] Currently, there are patients who self-administer aspirin to reduce the risk of ischemic heart disease, perhaps partly because information regarding the anticancer effect of the drug has begun to emerge in the community. In these groups, aspirin might be a good candidate for chemoprevention. In healthy individuals, younger age groups, and patients not receiving any other medications, regular aspirin use would probably lead to an unacceptable increased risk of gastrointestinal tract bleeding and hemorrhagic stroke.

It is important to know how patients presently use aspirin in the community. Vital data include how many patients self-administer aspirin, how many take aspirin on a physician's advice, and an understanding of the nature of compliance with aspirin therapy in the community. Although randomized controlled trials give valuable information regarding efficacy, they are not representative of how medications are realistically used by patients in the community.

Surprisingly, little information exists in the literature concerning aspirin use in the community and is mainly limited to retrospective studies focused on the use of aspirin in cardiovascular disease.[15] The aim of our study was to prospectively investigate aspirin use, compliance, and awareness of its anticancer effect in our community.

METHODS

Prospective data were collected using questionnaires and chart reviews during a 1-year period from every patient attending our community general surgical clinic regarding aspirin use, comorbidities, adverse effects of aspirin, and awareness of the effect of aspirin against colorectal cancer. All patients were referred from local primary care practices in Carleton County, New Brunswick, Canada. Compliance was defined as full if the patient stated on the questionnaire s/he never or rarely missed a dose of aspirin. Noncompliance was registered for all other entries apart from this. We did not specifically ask why patients were taking aspirin in our study and did not inquire regarding income or class stratification.

Patients were asked on questionnaires if they were aware of the anticancer effect of aspirin and, if so, to list their sources of

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information. Concomitant use of other medications was recorded on a separate questionnaire given to all patients as part of hospital policy and was used to derive statistics for the number and the types of concurrent medications. Exclusion criteria included age younger than 18 years or older than 100 years. Patients were divided into 2 groups: Aspirin users and nonusers. All patients gave informed consent for the study.

Statistical analyses were performed with the unpaired *t*-test and the Fisher exact test using statistical software (SPSS version 16). The level of significance was set at 0.05.

RESULTS

Five hundred twenty patients were enrolled prospectively in the study. Allergy to aspirin or sensitivity was not disclosed by any patient. All patients were white. Table 1 shows the patients' characteristics by study group.

Aspirin Users

A total of 76.6% of patients were taking a daily aspirin dose of 81 mg; 5.8% of patients were taking a dose more than 300 mg; in 17.6%, the exact dose of aspirin being taken could not be determined. In fact, 32.9% of patients were not even aware of what dose of aspirin they were taking, although in some of these patients, the information was able to be determined from the medical record. Sixty-two percent of patients were taking aspirin on their physician's advice, and the rest were self-administering aspirin without a physician's recommendation.

Compliance with aspirin therapy was low, with 25.6% of patients stating they never or rarely missed a dose of aspirin. Another 39% admitted to missing doses weekly to monthly, and 3% never took aspirin despite it being prescribed. Less than 6% (5.8%) of patients taking aspirin reported adverse effects, including minor bruising, bleeding, or gastrointestinal upset. No serious complications were described.

Patients with diabetes mellitus were significantly more likely to be fully compliant with aspirin therapy compared with those without diabetes (p = 0.0028, Table 2). Age and sex were not significant factors in compliance.

Table 1. Characteristics of aspirin users vs nonusers

Characteristic	Aspirin users (N = 137)	Nonusers (N = 383)	p value (unpaired *t*-test)
Men:women ratio	1.11:1	1:1.84	NA
Mean age (range), y	65.8 (23-100)	53.3 (18-90)	< 0.001
Awareness of anticancer effect, %	9.5	4.7	0.06
Aspirin users in past/ceased treatment, %	NA	1	NA

NA = not applicable.

Nonusers

Patients not using aspirin were significantly more likely to be women, younger than age 40 years, have ischemic heart disease, have diabetes, and/or use more than 5 concurrent medications (Table 3). No significant difference was found between the groups in anticoagulant use, additional NSAID use, or current smoking/history of smoking (Table 3).

Knowledge of Anticancer Effect

Knowledge of aspirin's anticancer effect was low in both groups, especially nonusers (Table 1). There might be some modest degree of evidence for knowledge of anticancer effect in the aspirin users group because the p value was near 0.05; however, this finding cannot be taken as significant. The main sources of information regarding the anticancer effect were media or the Internet.

Table 2. Compliance with therapy in aspirin users group

Factor	p value[a]
Age	0.22
Sex	0.24
Diabetes mellitus	0.0028
Ischemic heart disease	0.06
Use of > 5 medications	0.07

[a] Fisher exact test.

Table 3. Significant differences of nonusers of aspirin versus aspirin users

Characteristic	p value[a]
Female sex	< 0.0005
Age < 40 y	< 0.0001
Ischemic heart disease	0.002
Diabetes	< 0.0005
Use of > 5 medications	< 0.0005
Smoker/ex-smoker	0.19
Anticoagulant use	0.51
Additional NSAID use	0.20

[a] Fisher exact test; nonusers compared with aspirin users.
NSAID = nonsteroidal anti-inflammatory drug.

DISCUSSION

Noncompliance occurs when patients do not follow recommended treatment plans. Underuse occurs when medications are used or prescribed less than would be expected.[15] Compliance in our study was self-reported. Retrospective reporting can be inaccurate because patients may overestimate the degree of compliance with treatment.[16-18] We relied on self-reporting because other ways of measuring compliance (eg, pill counting, measurement of serum levels) were not applicable to the design of our study and were logistically difficult to implement. Patient reporting, however, has been shown to be more accurate than clinician reporting.[19,20] Physicians may exaggerate compliance or find it difficult to estimate, particularly with long-term treatment regimens.

In our study, 62% of the aspirin users were taking the medication under physician advice, probably for prevention of cardiovascular disease. The rest were self-administering aspirin. We did not explore reasons for aspirin use in this specific group, but with knowledge of the anticancer effect at only 9.5% in this group, it is possible that patients self-administered aspirin for cardiovascular reasons or perhaps for analgesia. We note that we did not specifically ask why patients were taking aspirin in our study, and this is perhaps a limitation of our work, because it may have given an insight into compliance.

Compliance was significantly associated with the presence of diabetes mellitus. Age and sex were not significantly associated with compliance. In our study, aspirin *nonusers* were significantly associated with age and presence of diabetes and cardiac

disease, but in aspirin users, *better compliance* was associated with diabetes. It is possible that the aspirin users represent a group with substantial disease that is either more health conscious or has better relationships with primary health care practitioners. These factors have been demonstrated to improve adherence to medical advice.[21] This group of patients may have had more specialist involvement in their care. Patients managed by cardiologists have significantly better compliance, including with aspirin therapy.[22]

A recent systematic review examined factors influencing noncompliance with antihypertensive agents.[23] The regimens for antihypertensive medications are similar to aspirin in various ways, including that they are taken daily at a low dose for long periods (years). Three key factors were found to be consistently related to noncompliance: Medication cost, adverse effects, and the nature of the physician-patient relationship.[23] Some other factors determined to be potentially relevant were racial/ethnic minority status, marital status, depression, a history of cardiovascular disease, and multiple dosing regimens.

In our rural community, we believe that cost plays a major role in compliance and underuse of aspirin. Although aspirin is fairly inexpensive and is available over the counter, cost is probably still an issue for many of our patients who are from very low-income families. Additionally, the lack of an obvious benefit while taking a medication long term may lead to underuse and poor compliance. Although we did not specifically look at income and social class and their impact on the use of aspirin in our study, this needs more analysis in our sample and will be the focus of ongoing work. Some evidence suggests that if patients know they will need to take medication regularly for years, compliance suffers, particularly if regimens are complex.[24-26]

Reviewing the aspirin users group, there was variability in the dosing regimens prescribed, ranging from 81 mg once daily to nearly 6% taking more than 300 mg. This range indicates there may be issues with understanding what constitutes an effective aspirin regimen for primary and secondary prevention. This issue needs urgent exploration because higher doses of aspirin are associated with greater risks of complications of bleeding and peptic ulceration.[14]

Adverse effects can reduce compliance with most medications, but this effect is not as strong as others, including the physician-patient relationship.[26] Low-dose aspirin is relatively well tolerated, reflected by the low incidence of adverse effects in our study (5.8%). Access to primary care and the physician-patient relationship could be key factors explaining noncompliance in our study. In patients using prescribed medications for psychiatric illness, 74% who form weak or poor alliances with their physician at 6 months fail to adhere to medication use during the following year and a half.[27]

Understanding and memory of consultations can affect satisfaction with the encounter, which in turn affects compliance.[28] Organizational factors, such as waiting time, comfort of seating, noncohesive staff, and inconvenient appointment times, are also relevant.[29,30] Although physicians seldom attribute a patient's noncompliance to their own communication style, there is evidence to demonstrate otherwise. The type of language used, quality of information given, and nature of the instructions to take the medication, all affect compliance.[26,31] Nonadherence to a prescribed treatment may reflect an effort by the patient to restore control lost to the illness, its treatment, and an unsatisfactory physician-patient relationship.[26] Teaching patients to gain control over their health issues can result in improved adherence.[32]

How patients perceive illness can affect compliance with using medication. In the context of a prevention strategy, a healthy patient may not see the benefit of taking medications daily because there is no immediate gain. In chronic disease with pervasive symptoms, another addition to a regimen that does little to improve ongoing quality of life may seem unnecessary. This coupled with unsatisfactory consultations can reduce compliance.

Underuse of Aspirin

Nonuse was significantly associated with women younger than age 40 years, the presence of ischemic heart disease or diabetes, and polypharmacy. Underuse of cardiac and other medications has previously been shown to be associated with older age, female sex, diabetes, and symptomatic cardiac disease or intervention.[33-37] Other risk factors in these studies included ethnicity, being overweight, poor education, polypharmacy, and receiving dual antiplatelet therapy. Unfortunately, these groups are also representative of individuals who would derive the most benefit from primary or secondary prevention.

Women are less likely than men to be adherent in their long-term use of medications and less likely to receive the medication treatment and monitoring recommended by clinical guidelines.[36] It has been indicated that an individual's sex influences adherence. Women and men differ in their health beliefs and health behaviors and also may have different attitudes toward medications, with nonadherence appearing to be a more consistent phenomenon in women.[38] On a population basis, women and men can differ in educational level, employment, income, and disease patterns.[39] There is some evidence that women are more likely to obtain a prescription but then not fill it.[40]

Previous studies have also found that adverse effects of medications can be a reason for nonadherence in women.[39,41] Although women and men seem to report similar numbers of adverse effects, women use adverse effects as the reason for noncompliance almost twice as often as men.[42] This might correlate to underuse of medications for prevention of disease, particularly if there is no immediate perceived benefit. Other studies have found that women have a higher risk for development of adverse effects with medication.[43] It is possible they are more sensitive to drugs compared with men because of pharmacokinetic differences, wrong doses, or unsuitable medications more often than men.

The reasons for underuse of aspirin in our study population are likely to be multifactorial but are likely to include the same issues as with compliance. These reasons include problems in the nature of the physician-patient relationship, poor access to specialty care, poverty, lack of adequate health information, and lack of clear communication strategies for primary and secondary prevention in the physician's office. In our community, these issues are common, and all have been shown to correlate with underuse in the aforementioned studies.

Interestingly, we found that polypharmacy was associated with nonuse

of aspirin. It has previously been shown that when patients take just 1 medication, nonadherence is around 15%; when 2 or 3 drugs are prescribed, nonadherence rates can increase to 25%, and with 5 or more medications, rates of nonadherence simply owing to drug error alone can be as high as 35%.[26,44] It is not clear how this translates to underuse or nonuse from the patient's point of view. It may be possible that in the context of polypharmacy and chronic disease, the less likely a patient will be to use another medication, even if recommended by his/her family physician, particularly in the absence of immediate benefit.[45,46] This hypothesis requires further testing in a prospective enrolled study.

Knowledge of Anticancer Effect

There was an interesting hint in our study findings that patients using aspirin might be more aware of the anticancer effect of aspirin compared with nonusers. We would like to reaffirm that this was not a significant finding, as is true of the other instances in our study in which the value of p was near 0.05 and can therefore not be deemed significant, according to Wood et al.[47]

The anticancer effect of aspirin is well documented in the medical literature and has recently surfaced in the general media.[48] It appears, however, this information has not yet translated into awareness at the physician-patient interface. Previous studies found that although patients may seek health information from the Internet and various other sources, the quality of the physician-patient relationship is more valuable in terms of access to health knowledge.[49] The various means of disseminating information in the modern era represent a potential opportunity for increasing patient education about the anticancer effect of aspirin.

CONCLUSION

For a strategy of chemoprevention of colorectal cancer with aspirin to be successful, the drug must be taken at the physician-recommended dose without fail, regularly, and long term. The risks of taking the medication must be lower than the perceived benefit.

Results of recent studies have suggested that the risk of major bleeding events with aspirin may be higher than previously considered and may equally balance or approach any cardiovascular benefit.[50,51] Chemoprophylaxis seems to make sense in patients already prescribed aspirin for prevention of cardiac disease because a potential risk reduction of colorectal cancer of up to 27% might outweigh the percentage risks of adverse effects of aspirin. This decision would need a balanced discussion of harms vs benefits with the patient.

Underuse and nonadherence to medications have substantial cost and health implications for society. We hope our results, taken in the context that they represent only our local community, will help inform clinicians of groups that are most vulnerable for noncompliance and underuse of aspirin and allow them to develop and target effective prevention strategies. In the future, we would like to examine knowledge of aspirin's anticancer effect in patients in general, and in a wider physician population. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Author Contributions

Gurpreet Singh Ranger, MD, conceived the study idea, designed the study and questionnaire, saw the patients, and drafted the final manuscript. Cindy McKinley-Brown, RN, statistically analyzed the data, and provided critical insight into the paper. Emma Rogerson helped review and submit the final manuscript. Krystal Schimp-Manuel distributed and organized the collection of the questionnaires. All authors have given final approval to the manuscript.

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References

1. Singh Ranger G. The role of aspirin in colorectal cancer chemoprevention. Crit Rev Oncol Hematol 2016 Aug;104:87-90. DOI: https://doi.org/10.1016/j.critrevonc.2016.05.011 PMID:27289249
2. Singh-Ranger G, Mokbel K. The role of cyclooxygenase-2 (COX-2) in breast cancer, and implications of COX-2 inhibition. Eur J Surg Oncol 2002 Nov;28(7):729-37. DOI: https://doi.org/10.1053/ejso.2002.1329 PMID:12431470
3. Singh-Ranger G, Salhab M, Mokbel K. The role of cyclooxygenase-2 in breast cancer: Review [review]. Breast Cancer Res Treat 2008 May;109(2):189-98. DOI: https://doi.org/10.1007/s10549-007-9641-5 PMID:17624587
4. Pugh S, Thomas GA. Patients with adenomatous polyps and carcinomas have increased colonic mucosal prostaglandin E2. Gut 1994 May;35(5):675-8. DOI: https://doi.org/10.1136/gut.35.5.675 PMID:8200564
5. Herschman HR. Prostaglandin synthase 2. Biochim Biophys Acta 1996 Jan 5;1299(1):125-40. DOI: https://doi.org/10.1016/0005-2760(95)00194-8
6. Appleby SB, Ristimäki A, Neilson K, Narko K, Hla T. Structure of the human cyclo-oxygenase-2 gene. Biochem J 1994 Sep 15;302(Pt 3):723-7. DOI: https://doi.org/10.1042/bj3020723
7. Gately S. The contributions of cyclooxygenase-2 to tumor angiogenesis. Cancer Metastasis Rev 2000;19(1-2):19-27. DOI: https://doi.org/10.1023/A:1026575610124 PMID:11191059
8. Marnett LJ. Aspirin and related nonsteroidal anti-inflammatory drugs as chemopreventive agents against colon cancer. Prev Med 1995 Mar;24(2):103-6. DOI: https://doi.org/10.1006/pmed.1995.1017 PMID:7597006
9. Prescott SM, Fitzpatrick FA. Cyclooxygenase-2 and carcinogenesis. Biochim Biophys Acta 2000 Mar 27;1470(2):M69-78. DOI: https://doi.org/10.1016/S0304-419X(00)00006-8
10. Wiese FW, Thompson PA, Kadlubar FF. Carcinogen substrate specificity of human COX-1 and COX-2. Carcinogenesis 2001 Jan;22(1):5-10. DOI: https://doi.org/10.1093/carcin/22.1.5 PMID:11159734
11. Cook NR, Lee IM, Zhang SM, et al. Alternate-day, low-dose aspirin and cancer risk: Long-term observational follow-up of a randomized trial. Ann Intern Med. 2013;16;159(2):77-85. DOI: https://doi.org/10.7326/0003-4819-159-2-201307160-00002
12. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010 Nov 20;376(9754):1741-50. DOI: https://doi.org/10.1016/s0140-6736(10)61543-7 PMID: 20970847
13. Friis S, Riis AH, Erichsen R, Baron JA. Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: A population-based, case-control study. Ann Intern Med. 2015 Sep 1;163(5):347-55. DOI: https://doi.org/10.7326/m15-0039 PMID: 26302241
14. Ranger GS. Current concepts in colorectal cancer prevention with cyclooxygenase inhibitors. Anticancer Res 2014 Nov;34(11):6277-82. PMID:25368225
15. Biondi-Zoccai G, Wu Y, Serrano CV Jr, Frati G, Agostoni P, Abbate A. Aspirin underuse, non-compliance or cessation: Definition, extent, impact and potential solutions in the primary and secondary prevention of cardiovascular disease. Int J Cardiol 2015 Mar 1;182:148-54. DOI: https://doi.org/10.1016/j.ijcard.2014.12.091 PMID:25577751
16. Caron HS, Roth HP. Objective assessment of cooperation with an ulcer diet: Relation to antacid intake and to assigned physician. Am J Med Sci 1971 Feb;261(2):61-6. DOI: https://doi.org/10.1097/00000441-197102000-00001 PMID:5550135
17. Velligan DI, Wang M, Diamond P, et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. Psychiatr Serv 2007 Sep;58(9):1187-92. DOI: https://doi.org/10.1176/ps.2007.58.9.1187 PMID:17766564
18. Byerly MJ, Thompson A, Carmody T, et al. Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia. Psychiatr Serv 2007 Jun;58(6):844-7. DOI: https://doi.org/10.1176/ps.2007.58.6.844 PMID:17535946

19. Taylor DW. Chapter 6: A test of the health belief model in hypertension. In: Compliance in health care. Haynes B, Sackett DL, editors. Baltimore, MD: Johns Hopkins University Press: 1979; p 103-9.
20. Orme CM, Binik YM. Consistency of adherence across regimen demands. Health Psychol 1989;8(1):27-43. DOI: https://doi.org/10.1037/0278-6133.8.1.27 PMID:2707222
21. Francis V, Korsch BM, Morris MJ. Gaps in doctor-patient communication. Patients' response to medical advice. N Engl J Med 1969 Mar 6;280(10):535-40. DOI: https://doi.org/10.1056/NEJM196903062801004 PMID:5764453
22. Short D, Frischer M, Bashford J, Ashcroft D. Why are eligible patients not prescribed aspirin in primary care? A qualitative study indicating measures for improvement. BMC Fam Pract 2003 Jul 18;18;4:9. DOI: https://doi.org/10.1186/1471-2296-4-9 PMCID: PMC183829
23. van der Laan DM, Elders PJM, Boons CCLM, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: A systematic review. J Hum Hypertens 2017 Nov;31(11):687-94. DOI: https://doi.org/10.1038/jhh.2017.48 PMID:28660885
24. Reichgott MJ, Simons-Morton BG. Strategies to improve patient compliance with antihypertensive therapy. Prim Care 1983 Mar;10(1):21-7. PMID:6553937
25. Julius RJ, Novitsky MA Jr, Dubin WR. Medication adherence: A review of the literature and implications for clinical practice. J Psychiatr Pract 2009 Jan;15(1):34-44. DOI: https://doi.org/10.1097/01.pra.0000344917.43780.77 PMID:19182563
26. O'Brien MK, Petrie K, Raeburn J. Adherence to medication regimens: Updating a complex medical issue. Med Care Rev 1992 Winter;49(4):435-54. DOI: https://doi.org/10.1177/002570879204900403 PMID:10123082
27. Frank AF, Gunderson JG. The role of the therapeutic alliance in the treatment of schizophrenia. Relationship to course and outcome. Arch Gen Psychiatry 1990 Mar;47(3):228-36. DOI: https://doi.org/10.1001/archpsyc.1990.01810150028006 PMID:1968329
28. Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatr Serv 2007 Jun;58(6):855-63. DOI: https://doi.org/10.1176/ps.2007.58.6.855 PMID:17535948
29. Dunbar JM, Agras WS. Compliance with Medical Instructions. In: Ferguson JM, Taylor CB, editors. Comprehensive handbook of behavioral medicine. Vol 3. New York, NY; Spectrum: 1980.
30. Fielding JE, Breslow L. Health promotion programs sponsored by California employers. Am J Public Health 1983 May;73(5):538-42. DOI: https://doi.org/10.2105/AJPH.73.5.538 PMID:6837818
31. Jacobs J. Perplexity, confusion and suspicion: A study of selected forms of doctor-patient interactions. Soc Sci Med 1971 Apr;5(2):151-7. DOI: https://doi.org/10.1016/0037-7856(71)90095-3 PMID:5088723
32. Ley P, Bradshaw PW, Kincey JA, Atherton ST. Increasing patients' satisfaction with communications. Br J Soc Clin Psychol 1976 Nov;15(4):403-13. DOI: https://doi.org/10.1111/j.2044-8260.1976.tb00052.x PMID:1000148
33. Choudhry NK, Setoguchi S, Levin R, Winkelmayer WC, Shrank WH. Trends in adherence to secondary prevention medications in elderly post-myocardial infarction patients. Pharmacoepidemiol Drug Saf 2008 Dec;17(12):1189-96. DOI: https://doi.org/10.1002/pds.1671 PMID:18956426
34. VanWormer JJ, Greenlee RT, McBride PE, et al. Aspirin for primary prevention of CVD: Are the right people using it? J Fam Pract 2012 Sep;61(9):525-32. PMID:23000660
35. Stafford RS, Monti V, Ma J. Underutilization of aspirin persists in US ambulatory care for the secondary and primary prevention of cardiovascular disease. PLoS Med 2005 Dec;2(12):e353. DOI: https://doi.org/10.1371/journal.pmed.0020353 PMID:16277554
36. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J Womens Health (Larchmt) 2014 Feb;23(2):112-9. DOI: https://doi.org/10.1089/jwh.2012.3972 PMID:24206025
37. Niu S, Zhao D, Zhu J, et al.; BRIG project. The association between socioeconomic status of high-risk patients with coronary heart disease and the treatment rates of evidence-based medicine for coronary heart disease secondary prevention in China: Results from the Bridging the Gap on CHD Secondary Prevention in China (BRIG) Project. Am Heart J 2009 Apr;157(4):709-15.e1. DOI: https://doi.org/10.1016/j.ahj.2008.12.009 PMID:19332200
38. Thunander Sundbom L, Bingefors K. Women and men report different behaviours in, and reasons for medication non-adherence: A nationwide Swedish survey. Pharm Pract (Granada) 2012 Oct;10(4):207-21. DOI: https://doi.org/10.4321/S1886-36552012000400005 PMID:24155839
39. Applebaum AJ, Richardson MA, Brady SM, Brief DJ, Keane TM. Gender and other psychosocial factors as predictors of adherence to highly active antiretroviral therapy (HAART) in adults with comorbid HIV/AIDS, psychiatric and substance-related disorder. AIDS Behav 2009 Feb;13(1):60-5. DOI: https://doi.org/10.1007/s10461-008-9441-x PMID:18690532
40. Rivera CM, Song J, Copeland L, Buirge C, Ory M, McNeal CJ. Underuse of aspirin for primary and secondary prevention of cardiovascular disease events in women. J Womens Health (Larchmt) 2012 Apr;21(4):379-87. DOI: https://doi.org/10.1089/jwh.2011.2990 PMID:22303820
41. Pound P, Britten N, Morgan M, et al. Resisting medicines: A synthesis of qualitative studies of medicine taking. Soc Sci Med 2005 Jul;61(1):133-55. DOI: https://doi.org/10.1016/j.socscimed.2004.11.063 PMID:15847968
42. Isacson D, Johansson L, Bingefors K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. Ann Pharmacother 2008 Mar;42(3):347-53. DOI: https://doi.org/10.1345/aph.1K488 PMID:18303136
43. Tran HV, Waring ME, McManus DD, et al. Underuse of effective cardiac medications among women, middle-aged adults, and racial/ethnic minorities with coronary artery disease (from the National Health and Nutrition Examination Survey 2005 to 2014). Am J Cardiol 2017 Oct 15;120(8):1223-9. DOI: https://doi.org/10.1016/j.amjcard.2017.07.004 PMID:28822562
44. Koltun A, Stone GC. Past and current trends in patient noncompliance research: Focus on diseases, regimens-programs, and provider-disciplines. J Compliance Health Care 1986 Spring;1(1):21-32. PMID:10277144
45. Turk DC, Salovey P, Litt MD. Adherence: A cognitive-behavioral perspective. In: Gerber KE, Nehemkis AM, editors. Compliance: The dilemma of the chronically ill. New York, NY: Springer; 1985.
46. Nehemkis AM, Gerber KE. Compliance and the quality of survival. In: Gerber KE, Nehemkis AM, editors. Compliance: The dilemma of the chronically ill. New York, NY: Springer; 1985.
47. Wood J, Freemantle N, King M, Nazareth I. Trap of trends to statistical significance: Likelihood of near significant P value becoming more significant with extra data. BMJ 2014 Mar 31;348:g2215. DOI: https://doi.org/10.1136/bmj.g2215 PMID:24687314
48. Boggs W. An aspirin a day—for years—may keep colon cancer away [Internet]. New York, NY: Reuters; 2015 Aug 25 [cited 2019 Oct 24]. Available from: www.reuters.com/article/us-health-colorectalcancer-prevention/an-aspirin-a-day-for-years-may-keep-colon-cancer-away-idUSKCN0QT2CV20150825
49. Laugesen J, Hassanein K, Yuan Y. The impact of internet health information on patient compliance: A research model and an empirical study. J Med Internet Res 2015 Jun 11;17(6):e143. DOI: https://doi.org/10.2196/jmir.4333 PMID:26068214
50. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: A systematic review and meta-analysis. JAMA 2019 Jan 22;321(3):277-87. DOI: https://doi.org/10.1001/jama.2018.20578 PMID:30667501 Erratum in: JAMA 2019 June 11;321(22):2245. DOI: https//10.1001/jama.2019.3941
51. Bowman L, Mafham M, Wallendszus K, et al, ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018 Oct 18;379(16):1529-39. DOI: https://doi.org/10.1056/NEJMoa1804988 PMID:30146931