β-Blockers and Depression: The More the Murkier?

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OBJECTIVE: To review the literature regarding the purported association between oral ingestion of β-blocker drugs and depressed mood.

DATA SOURCE: MEDLINE was searched for published articles using the key words propranolol, atenolol, metoprolol, nadolol, timolol, β-blocker, β-adrenergic antagonist, or β-adrenergic blocker in combination with the key words depression, depressive symptomatology, major depressive disorder, or depressed mood from January 1966 through December 1996.

DATA SYNTHESIS: Findings regarding the association are equivocal. Plausible explanations include study design, case definition, and confounding disease states. Most of the evidence supporting an association has used case series and case reports. Findings from cross-sectional observational studies and case–control studies are equivocal. Case definition and measurement instruments may partially explain these inconsistencies. Studies using a diagnosis of depression generally do not support the relationship. Trials using depressive symptoms are about evenly split, but they have generally enrolled a small number of patients and have questionable statistical power. Studies defining antidepressant prescriptions dispensed as a marker for depression generally support the association. Evidence exists both for and against the hypothesis that lipophilic β-blockers cause more depression than do hydrophilic β-blockers.

CONCLUSIONS: β-Blockers may have been unjustly associated with depression and their use avoided for that reason. Future studies into the association between depression and β-blocker use should evaluate whether the association is affected by case definition and study design characteristics, including disease, dose–response, bias, measurement error, or ability to precisely measure the length of the exposure.

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CASE REPORTS AND CASE SERIES describing depression among patients taking propranolol appeared as early as 1967.[1-3] Waal[1] reported a series of 20 persons with "depressive symptoms" among 89 patients being treated with propranolol for hypertension and found the incidence of depression as high as 50% among patients prescribed more than 120 mg/d. Another case series[2] and accumulation of the data from nine trials[3] both claimed to substantiate the association.

However, claims for the association are not unanimous and, despite a relatively large number of publications, the conclusions remain unclear. While the central nervous system (CNS) adverse effects of β-blockers are certain,[4] studies have questioned whether the purported depression is caused by the drugs, whether it is really clinical depression, and whether it occurs more frequently than in similar populations not taking β-blockers.[5-8] For example, an early review of the first 1500 persons treated with (oral) propranolol mentions only 1 case of "mental confusion," 7 cases of "sleeplessness," and 18 cases of "tiredness and drowsiness."[8] Depression, per se, was not listed among the reported adverse effects. Similarly, Carney et al.[6] postulated that the pattern of depression-like adverse effects may not be sufficient to meet the criteria for major depressive disorders as defined in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised (DSM-III-R)*.[9] They concluded that the incidence of major depressive syndrome among patients receiving β-blockers was no greater than among patients with similar medical disorders receiving other medications.[6]

Given the inconclusive findings about the purported association between oral ingestion of β-blocker drugs and depressed mood, this article provides plausible explanations for the contradictory findings and makes recommendations for future research.

Literature Synthesis

This review highlights methodologic, clinical, and pharmacodynamic issues in studies found in the published literature (Table 1).[2,6,10-33] Each study's design was summarized to indicate whether it was blinded or randomized and its type of control (i.e., case–control, crossover, active, placebo). It also considers the case definition of depression, specific β-blocker used, its dose, the duration of treatment, and various study design biases. It is conceivable that the findings of various studies may differ, depending on these biases.

STUDY DESIGN

Case Studies

The case study is the weakest study design, and most of the early published reports in support of the association were case studies or case series reports. Three typical case reports illustrate the evidence.[10,14,16]

Petrie et al.[10] described three patients with episodes of major depression after administration of propranolol for medical illnesses. The depressive episodes were dose-dependent (e.g., >80 mg/d) and promptly remitted when propranolol was discontinued. In one case, the patient's depression returned with the readministration of propranolol. In all three cases, the symptoms were distinguishable from fatigue and lassitude and were classified as major depressive episodes according to *DSM-III* criteria.

Another study[14] described two cases. In one case, a 63-year-old woman had one episode of depression 30 years earlier and a family history of depression. She was administered low-dose propranolol (20 mg/d) for angina. Depressive symptoms appeared and she attempted suicide. The propranolol was discontinued and antidepressant therapy was begun. Six months later, the antidepressant was tapered to discontinuation (the case report does not say how long it was discontinued) and she was prescribed a small dosage of metoprolol. Within days of starting the β-blocker, the patient reported that she did not feel well. She "recovered" when she stopped taking the metoprolol. In a similar case, a 62-year-old man was started on low-dose propranolol (30 mg/d) for hypertension. A depressive episode spontaneously cleared when he discontinued the propranolol. Two weeks after resuming propranolol, he reported severe depression. He discontinued the propranolol, and the depressive symptoms disappeared.

Parker[16] described a 42-year-old woman without a history of depression who experienced depression when given propranolol 80 mg/d. The dosage was reduced and symptoms stopped. The symptoms reappeared when she resumed the previous dose. She was placed on atenolol and the symptoms resolved.

Several characteristics of these case reports argue persuasively for the association between depression and β-blocker administration. For example, three of the case reports included a rechallenge of the medication for the patient.[10,14,16] In one case, the patient was rechallenged in a randomized, controlled fashion.[10] Moreover, several of the patients were without a prior history of depression[10,16] and the depression was severe enough that the patients contemplated or attempted suicide.

However, there are indications that some patients were predisposed to depression and the association could be spurious. For example, some patients reported earlier episodes of depression or a family history of depression.[14,19] The depression and drug-taking may have been confounded with other disease(s) that the patients reported. For example, patients in these case reports[10] also had cardiovascular diseases and hypertension.[10,14,16] Heart conditions and high blood pressure place patients at increased risk of depression.[26,34] Finally, in one case study,[14] the recurrence of the depressive symptoms might have been associated with the withdrawal of the antidepressant medication, not the resumption of the β-blocker.

The case report evidence regarding a causal association between propranolol and depression is persuasive. While case reports are excellent for generating hypotheses to be tested by stronger study designs, they have less power to assign causation.

Quasi-experimental and Experimental Study Designs

Since the mid-1980s, more rigorous studies have tested hypotheses suggested by the case reports. Studies supporting the existence of an association have used cross-sectional[18] and retrospective cohort methodologies.[28] An age-specific association was found among coronary artery disease survivors younger than 65 years of age.[26] A prospective double-blind, randomized, placebo-controlled trial of hypertensive men found a positive association between depressive symptomatology and drug dosage.[17] Other randomized controlled studies found that patients taking propranolol scored more poorly on a measure of depressive symptomatology[35] and had more physician visits for undefined "depression."[13]

However, a case–control study found no greater risk for case patients with a depression diagnosis or electroconvulsive therapy.[30] A cross-sectional study[6] methodology of patients with suspected coronary artery disease found fewer episodes of major depressive disorders and less depressive symptomatology among patients taking β-blockers. A prospective study[29] of a convenience sample of hypertensive men found that β-blocker therapy did not cause any more depressive symptomatology than did any other antihypertensive treatment. Other studies[25,27,31] using randomized, double-blind, placebo-controlled trials found no statistically significant association between depression and β-blocker use, although one found that metoprolol was slightly more implicated in development of depression.[25] Similarly, 11 of 34 patients in a double-blind crossover study had scores on the Beck Depression Inventory (BDI) indicative of active depression at some time during the trial; however, there was no demonstrable drug effect.[27] Several large prospective trials[7,20,21] of the effectiveness of β-blockers in other medical conditions (e.g., post-myocardial infarction) found no difference in the rate of depressive symptoms as an adverse effect of treatment. Finally, a retrospective cohort study[33] found no significant difference in the risk of depression between new users of non-β-blockers and propranolol or all β-blockers combined.

Table 1. Studies Examining the Relationship Between β-Blockers and Depression

REFERENCE	STUDY DESIGN	DEPRESSION MEASURE	TYPE OF β-BLOCKER (n)	COMPARISON GROUP (n)	STATISTICAL FINDING	MORBID/ COMORBIDITY	DEPRESSION HISTORY
Petrie et al. (1982)[10]	case report	depression diagnosis	propranolol (3)	NA (NA)	NA	cardiac problem	2 no, 1 yes
McNeil et al. (1982)[11]	case report	depression diagnosis	propranolol (1)	NA (NA)	NA	post-MI	no
Nolan (1982)[12]	case report	depression diagnosis	timolol ophthalmic (1)	NA (NA)	NA	glaucoma, diabetes	not stated
VA Coop. Study Group (1982)[13]	DB, RCT	depression not defined	propranolol (125)	hydrochlorothiazide (177)	$p < 0.004$	HT	not stated
Cremona-Barbaro (1983)[14]	case report	depression diagnosis	propranolol (2)	NA (NA)	NA	angina, HT	2 yes
Stoudemire et al. (1984)[15]	randomized cohort	Zung SDS	propranolol + thiazide (11)	thiazide only (13) thiazide + prazosin (11)	$p = 0.316$ $p = 0.205$[a]	HT	not stated
Parker (1985)[16]	case report	depression diagnosis	propranolol (2)	NA (NA)	NA	HT, angina	none
Pollack et al. (1985)[2]	case report	depression and symptoms	propranolol (3)	NA (NA)	NA	HT	2 no, 1 yes
Potempa et al. (1986)[17]	DB, crossover	BDI	propranolol (19)	placebo (19)	$p = 0.002$	HT	not stated
Avorn et al. (1986)[18]	cross-sectional	ADT	β-blocker[b] (8235) metoprolol (NR) propranolol (NR) nadolol (NR) propranolol[e] (2214)	hypoglycemia (NR) hydralazine (NR) hydralazine (NR) hydralazine (NR) hydralazine (NR)	1.5 (1.4–1.6)[c] 1.5 (1.3–1.8)[c] 1.5 (1.4–1.7)[c] 2.0 (1.7–2.3)[c] 1.2 (1.0–1.5)[d] for ≥65 y	not stated	not stated
Griffin and Friedman (1986)[19]	observational	Hamilton–Hudson generalized content	propranolol (34)	NA (NA)	NA	HT, angina, post-MI arrhythmia	14 yes, 20 no
Carney et al. (1987)[6]	cross-sectional	BDI	not stated (39)	calcium-channel blocker (36)	$t = 0.64$ $p = 0.52$	CAD	36%
Davis et al. (1987)[20]	RCT	single question			$\chi^2 = 0.39$	post-MI	not stated
Hjalmarson (1987)[21]	RCT	single question	propranolol (1916)	placebo (1921)	$p > 0.05$		
Fodor et al. (1987)[22]	single-blind crossover	depressed mood — not defined	propranolol (52)	atenolol (52) (crossover)	$p < 0.01$	HT	not stated
Blumenthal et al. (1988)[23]	random, DB, cohort	POMS	atenolol (8) propranolol (9)	placebo (9)	$p > 0.05$[a]	HT	not stated
Conant et al. (1989)[24]	random, DB, crossover	BDI POMS NIMH	propranolol (17)	atenolol (17) (crossover)	$p > 0.05$[a] $p < 0.05$[a] $p < 0.05$[a]	not stated	not stated
Goldstein et al. (1990)[25]	RCT	Zung SDS	metoprolol (43) metoprolol + diuretic (NR)	hydralazine (52) methyldopa (55) reserpine (39)	$p > 0.05$[a]	HT	not stated
Nickel et al. (1990)[26]	cohort	single question	not identified (n = 75, <65 y, n = 89, 65+ y)	no β-blocker (n = 109, <65); (n = 126, 65 y)	all RR 1.61; ≥65 y RR 1.33; <65 y RR 2.07	heart disease	not stated
Palac et al. (1990)[27]	random, DB, crossover	BDI	atenolol (34) propranolol (34)	drug free (crossover) (34)	$p > 0.05$[a] $p > 0.05$[a]	untreated HT	not stated
Thiessen et al. (1990)[28]	retrospective cohort	ADT	propranolol (1533) hydrophilic (437) lipophilic (1248) all β-blockers (3218)	hypoglycemics (1045) AHT (2195) diuretics (5289) no study drug (549 338)	4.8 (4.1–5.5) 0.8 (0.5–1.5) 0.9 (0.7–1.2) 2.1 (1.7–2.5)	not stated	prior ADT in 24% β-blockers; 11% control

ADT = antidepressant therapy; AHT = antihypertensive therapy; BDI = Beck Depression Inventory; CAD = coronary artery disease; DB = double-blind; HT = hypertension; NA = not applicable because there is no control group; NIMH = National Institute on Mental Health Depression scale; NR = not reported; POMS = Profile of Mood States; post-MI = post-myocardial infarction; RCT = randomized controlled trial; RR = risk ratio; SDS = Self-reported Depression Scale; VA Coop. Study Group = Veterans Administration Cooperative Study Group on Hypertensive Agents.

[a]Value of statistical test or probability not reported. Author(s) reported only as statistically nonsignificant or statistically significant.

[b]All three age-adjusted prevalence rate ratios (20–44, 45–64, ≥65 y) are greater than 1.0, and 95% CIs do not include 1.0.

[c]Prevalence rate ratio.

[d]Age-adjusted prevalence rate ratio.

[e]The adjusted prevalence rate ratios for the other age groups (20–44 and 45–64 y) are greater than 1.0, and the 95% CI does not include 1.0.

(*continued on page 702)*

In summary, the findings of studies with designs more rigorous than case reports were equivocal, although they supported the association less frequently than did case reports and case series.

DEFINING AND MEASURING "DEPRESSION"

Another plausible reason for equivocal results is the use of at least three measures of "depression" in the literature: (1) a clinical diagnosis of depression based on either *DSM* criteria or a diagnosis noted in the medical record, (2) presence of high levels of depressive symptoms as measured by a standardized instrument (e.g., Center for Epidemiologic Studies — Depression scale [CES-D]), and (3) dispensing of a prescription for an antidepressant. While all three measures have been interpreted as nearly equally valid measures of depression, they are not.[36,37] Therefore, it is worthwhile to examine them individually for differences in the consistency or strength of the association.

Depression Diagnosis

Depression definitions require depressed mood or loss of interest or pleasure, in addition to four or more of the following: (1) significant weight loss; (2) insomnia or hypersomnia; (3) psychomotor agitation or retardation; (4) fatigue or loss of energy; (5) feelings of worthlessness or excessive or inappropriate guilt; (6) diminished ability to think or concentrate; or (7) recurrent thoughts of death, or suicidal ideation or attempt.[38] None of the studies using a clinical diagnosis have supported the association. Carney et al.[6] found a lower proportion of 39 patients taking β-blockers had symptoms consistent with major depressive disorder according to *DSM-III-R* criteria, compared with 36 patients taking other medications (21% vs. 33%). The difference was not statistically significant because of the small sample size. Another study with modest statistical power used computerized medical records for case ascertainment.[33] The risk of major and minor depression, as defined by *DSM-III-R* criteria, was no different for new users

Table 1. Studies Examining the Relationship Between β-Blockers and Depression (continued)

REFERENCE	STUDY DESIGN	DEPRESSION MEASURE	TYPE OF β-BLOCKER (n)	COMPARISON GROUP (n)	STATISTICAL FINDING	MORBID/ COMORBIDITY	DEPRESSION HISTORY
Prisant et al. (1991)[29]	observational	Zung SDS	HL[f] (66) LL (20)	no drug (NR) reserpine (111) diuretics (NR)	p < 0.05[a] p > 0.05[a] p > 0.05[a]	HT	not stated
Bright and Everitt (1992)[30]	case–control	diagnosis ADT diagnosis ADT	any β-blocker (4302)	non-β-blocker users (8604)	1.2 (0.9–1.5)[g] 1.6 (1.3–1.9)[h] 0.7 (0.5–1.0)[i] 1.1 (0.9–1.4)[j]	not stated	not stated
Potempa et al. (1993)[31]	random, DB, crossover	BDI	propranolol (19) pindolol (19)	placebo (19) (crossover)	p > 0.05[a] p > 0.05[a]	HT	not stated
Johnson and Wallace (1995)[32]	retrospective cohort	ADT	propranolol 20–39 y (179) 40–59 y (243) ≥60 y (292) hydrophilic 20–39 y (104) 40–59 y (328) ≥60 y (431) lipophilic 20–39 y (71) 40–59 y (331) ≥60 y (483)	diuretic (4225)	 2.0 (1.1–3.5)[k] 1.7 (1.0–2.8)[k] 1.1 (0.6–2.0)[k] 1.0 (0.4–2.6)[k] 1.0 (0.5–1.8)[k] 1.0 (0.6–1.7)[k] 0.9 (0.3–3.0)[k] 1.0 (0.5–1.8)[k] 0.8 (0.5–1.4)[k]	not stated	not stated
Gerstman et al. (1996)[33]	retrospective cohort	major or minor depression diagnosis combined	propranolol (704) other β-blockers (587) all β-blockers (1291)	non-β-blocker (2491) users[l]	0.8 (0.1–2.7)[m] 0.8 (0.2–2.5)[m] 0.8 (0.3–1.9)[m]	HT thyroid cardiac headache tremor anxiety	none in previous 6 mo, not ascertained before

ADT = antidepressant therapy; BDI = Beck Depression Inventory; DB = double-blind; HL = high lipophilic; HT = hypertension; LL = low lipophilic; NR = not reported; SDS = Self-reported Depression Scale.

[a]Value of statistical test or probability not reported. Author(s) reported only as statistically nonsignificant or statistically significant.

[f]The difference in the Zung SDS was significantly significant ($p < 0.05$) for the comparison of white patients who were taking a high lipophilic β-blocker with white patients who were taking no antihypertensive. All other comparisons (e.g., African-American patients, high lipophilic β-blockers vs. reserpine and diuretics, and low lipophilic β-blockers vs. no antihypertensive, diuretics, and reserpine) were all statistically nonsignificant ($p > 0.05$).

[g]Crude odds ratio for depression diagnosis.

[h]Crude odds ratio for ≥2 claims for antidepressant.

[i]Adjusted odds ratio for depression diagnosis.

[j]Adjusted odds ratio for ≥2 claims antidepressant.

[k]Age-specific, sex-adjusted risk ratio for concurrent ADT dispensing.

[l]Angiotension-converting enzyme inhibitors, calcium-channel blockers, diuretic.

[m]Adjusted risk ratio for depression diagnosis.

of β-blockers and new users of non-β-blocker antihypertensives. Bright and Everitt,[30] using Medicaid automated claims data, found no difference in the risk for a depression diagnosis using ICD-9-CM codes (an indexing method for classifying morbidity data) or CPT codes (a numerical coding system that describes medical services and procedures) for electroconvulsive therapy. In fact, β-blockers were protective after three confounders (number of prescriptions filled for drugs other than β-blockers, benzodiazepine prescriptions, physician visits) were entered into the statistical model.

Finally, in randomized trials conducted to evaluate β-blockers' antihypertensive effectiveness, the number of patients with depression as an adverse treatment effect were reported. However, in each case the authors did not define depression.[13,39-45] For example, one study[13] claimed a difference in the proportion of patients reporting depression during visits; patients taking propranolol reported unspecified "mood changes" after 3 months in another study.[45] It is plausible that this poor specification of a depression diagnosis (e.g., not based on *DSM* criteria) and reliance on patients' self-reports of "depression" may be biasing the association.

One reason for the small number of studies using a diagnosis of depression is that it may not be required on outpatient claims, or care providers may be reluctant to note psychiatric diagnoses on claims.[46,47] Data collection regarding depression diagnoses, either from medical record abstraction or finding diagnosed cases in the community, is both difficult and expensive. Other potential problems with using depression diagnosis as the primary measure of depression include undiagnosed cases and poor interrater reliability of clinician-based diagnoses of depression.[48] For example, in nonpsychiatric medical settings, depressed patients may present with somatic complaints similar to everyday organic diseases and maladies. In these settings, physicians are apt to be more responsive to the presentation of physical symptoms.[49,50] Standardized instruments of depressive symptomatology are sometimes used to overcome these problems.

Depressive Symptomatology

Several standardized instruments have been used to identify persons with depressive symptomatology. Studies using the BDI have found evidence of both positive associations[17] and no association with β-blocker use.[6,27,31,51] No evidence for an association between depression and β-blocker use has been found using the Zung Self-reported Depression Scale (SDS).[15,25,29,52] Stoudemire et al.[15] found little difference on the Zung SDS in a study comparing a thiazide diuretic plus propranolol versus a thiazide diuretic plus prazosin. However, the authors acknowledged low statistical power. Goldstein et al.[25] found the Zung SDS score did not change significantly over a 6-month period from baseline to follow-up for patients taking metoprolol nor were their scores significantly different from the Zung SDS scores of those taking other medications. However, the proportion of persons with "clinical depression" (Zung score >50) in the metoprolol group rose from 29.2% to 37.2% over the 6 months. The sample sizes were relatively small (n = 43) and the finding of no difference may be due to the lack of power. Also, differences found in the dropout rates among the four groups may have attenuated the significance of the findings. For example, data were obtained for 79% of the patients taking hydralazine at the end of maintenance follow-up. The rate was 78%, 66%, and 60% for methyldopa, metoprolol, and reserpine, respectively. Those dropping out may have been more depressed at baseline or follow-up. In another study,[29] the average Zung SDS score was the highest among the patients taking β-blockers, even greater than those taking high-dose (>0.125 mg/d) reserpine.

A study[24] using the Profile of Mood States (POMS) as the measure of depressive symptomatology found significant differences between β-blockers (atenolol vs. propranolol), whereas a randomized clinical trial[23] of 26 hypertensive men using the POMS did not find a significant difference in scores after 2 weeks.

Three studies report results from single questions to measure depressive symptomatology. Two of these reports,[20,21] from the same Beta-Blocker Heart Attack Trial (BHAT), used patients' responses to a single item about the frequency that "depression interfered with work, recreation, or sleep." Patients taking β-blockers were no more likely to respond affirmatively than persons taking placebo, although the proportion was about 40% in both cases. Nickel et al.[26] used a single item from the General Well-Being Index,[52] "have you felt downhearted and blue during the last month?" Of the patients 65 years and older, 33% responded affirmatively, as did 40% of the patients younger than 65 years. While Berwick et al.[53] found this item to be a powerful "nonspecific" indicator of depression, the high proportion of persons classified as depressed in both studies raises concerns about using single items as indicators of major depressive syndrome. If a high proportion of false positives are misclassified by a powerful nonspecific indicator, a significant bias could result.

Several clinically and theoretically relevant questions emerge from these findings. A clinical diagnosis of depression requires both affective (hopelessness, despair, guilt) and somatic (sleep disturbances, lack of energy, irritability) symptoms.[38] Measures of depressive symptomatology have varying numbers and proportions of items referring to the affective and somatic dimensions. For example, the Geriatric Depression Scale was devised specifically to avoid somatic symptoms thought to complicate the identification of depression in the elderly with physical illness.

Case definition has implications for interpretation of the findings. For example, the two reports from the BHAT study[20,21] found no association between the single item measure of depressive symptomatology and β-blockers. However, they also used a single item about the effect of β-blockers on somatic symptoms: "unusual tiredness or fatigue during ordinary activities." Persons taking β-blockers were significantly more likely than patients taking placebo to answer affirmatively to that item. Two other studies[6,54] found that patients receiving β-blockers were significantly more likely to report somatic symptoms without mention of the affective symptoms of a clinical depression diagnosis. The CNS symptoms in these studies may be described

as "depression" without a clinically significant affective component.

The distinction between the affective and somatic dimensions of depressive symptomatology is important in interpreting the association. Fatigue occurs as an adverse effect with β-blockers in approximately 20% of patients.[54,55] Inaccurate diagnosis (when the underlying condition is something other than depression) may occur because patients and their provider focus on somatic concerns, such as extreme fatigue, listlessness, lethargy, sleep disturbances, and other somatic impairments.[56] The provider may prescribe multiple visits, procedures, and medications to treat the "depression-like" fatigue that is a CNS adverse effect of the antihypertensive drug.[56-58] This may be the reason for the consistent findings of a relationship with antidepressant dispensings, and why the relationship with depression diagnosis and depressive symptomatology is less consistent. This confounding may give poor estimates of the incidence and the strength and significance of the relationship.

Another explanation for the inconsistent findings is the time frame of the measures of depressive symptomatology. For example, the CES-D scale and BDI ask about symptoms in the previous week. Other studies[20,21] using depressive symptomatology have examined β-blocker use during "the year." In these studies, it is uncertain whether the drug was being taken at the same time that the depressive symptomatology measure was obtained.

Antidepressant Dispensing

Claims for antidepressant drugs would seem a priori to be both a specific and sensitive marker for depression. Using this assumption, several studies have used antidepressant medication claims as their measure of depression. In a large Medicaid population, persons taking a β-blocker were at a 50% greater risk of being dispensed an antidepressant compared with persons taking other medications for chronic diseases, including other antihypertensives.[18] Patients in the Thiessen et al.[28] study also had an increased risk of being dispensed an antidepressant; Johnson and Wallace[32] found the same relationship among 20- to 39-year-old patients, but not among older patients. When crude estimates were examined, Bright and Everitt[30] also found that patients dispensed an antidepressant were more likely to have taken β-blockers. However, controlling for other medication use and outpatient use resulted in null effect estimates. Ried et al.[59] found the risk of being dispensed an antidepressant greater among persons dispensed a β-blocker compared with the remainder of an elderly population (risk ratio [RR] 1.3; 95% CI 1.1 to 1.6), but the findings were less clear when comparing patients taking β-blockers with patients prescribed antihypertensive monotherapy (RR 1.4; 95% CI 0.8 to 2.6); patients prescribed multiple antihypertensive medications, usually including a diuretic (RR 1.2; 95% CI 1.0 to 1.5); or self-reported hypertensive patients who were not pharmacologically treated for hypertension (RR 1.30; 95% CI 0.9 to 1.9). In each case the risk was greater for patients taking β-blockers, but the confidence intervals were large because the sample sizes were small.

Antidepressant dispensings may not be a valid proxy for depression. In one study,[30] patients who were dispensed antidepressants had no other depression marker in their Medicaid record and less than half had more than one dispensing for an antidepressant. Since successful treatment of a major depressive episode generally requires prolonged therapy, the authors concluded that single-time users were not actually depressed and used the medication for another indication, had transient depressive symptoms, or were intolerant of adverse effects. They postulated that multiple users were more often true depression cases and that antidepressant dispensing was an inadequate measure of true clinical depression in the absence of other depression markers or indicators of care by a psychiatrist or psychologist.

This finding was supported by Ried et al.,[37] who compared antidepressant dispensings with diagnosis of depression in the medical record of an elderly cohort. On the positive side, the relationship between antidepressant dispensing and a diagnosis of depression in the medical record (RR 6.07; 95% CI 4.97 to 7.39) was significant. However, there was a large percentage of false positives (52%) and a low sensitivity (51%), indicating that the antidepressants were dispensed for other indications or for relief of depressive symptoms without a diagnosis in the medical record.

LIPOPHILIC VERSUS HYDROPHILIC β-BLOCKERS

Another possible reason for the confusion about the association between β-blockers and depression is the type of β-blocker. Lipophilic drugs cross the blood–brain barrier more readily than do the hydrophilic drugs. For example, lipophilic drugs such as propranolol have a brain-to-plasma concentration ratio of around 20, whereas hydrophilic drugs such as atenolol have a ratio of 0.2.[60] Hypothetically, the more hydrophilic β-blockers should have fewer CNS effects and should result in a lower association with depression. Combining hydrophilic and lipophilic β-blockers may attenuate the findings about the association. However, these findings also are mixed.

While atenolol and nadolol pass less readily through the blood–brain barrier, only minimal evidence exists that they cause less depression than does propranolol.[11] In one literature review,[54] general neuropsychological adverse effects were no more prevalent among patients receiving lipophilic β-blockers. Two randomized, double-blind trials of hypertensive men found little difference between atenolol and propranolol.[23,27] Two other studies[29,61] found the prevalence of depressive disorder between patients receiving lipophilic and hydrophilic β-blockers was not significantly different, although the number of patients in each study taking hydrophilic β-blockers was low (n = 9 and n = 20) and no post hoc power calculations were offered.

On the other hand, Russell and Schuckit[62] found nadolol (a hydrophilic β-blocker) to cause depression with therapeutic dosages; the symptoms resolved when the drug was discontinued. At therapeutic dosages (based on blood pressure control), two other studies[22,24] found the fraction of patients who were depressed was lower among those taking atenolol compared with those taking propranolol; another study[63] reported that propranolol had a significantly greater effect on mood, energy, and short-term memory. Finally,

Thiessen et al.[28] found no increase in the risk of being dispensed an antidepressant with any β-blocker other than propranolol.

OTHER POTENTIAL CONFOUNDERS AND BIASES

Dose–Response

The relationship between the β-blocker dose and the occurrence of depression has not been well studied. Several of the case studies[10,16] and a randomized controlled trial[17] found a positive dose–response relationship between major depression and dosage. In contrast, a case series report[19] and a clinical trial[31] found a negative relationship.

On the other hand, another study[61] concluded that the CNS effects of β-blockers were elicited at even relatively low serum concentrations and concluded that they were not dose-dependent. This finding is consistent with a literature review[64] that compared metoprolol (lipophilic) and atenolol (hydrophilic). It concluded the CNS adverse effects reported for the two drugs were not significantly different. Also pertinent is the literature regarding the occurrence of depression-like adverse effects with topical β-blockers used in the treatment of glaucoma.[12,65] Both of these findings suggest the association may not be dose-dependent.[60]

Disease Type and Comorbidities

Other underlying disease states and comorbidities may confound or bias the relationship between β-blockers and depression. A reason is that the prevalence of depression is higher among persons with different disease states compared with population-based surveys. For example, in the Epidemiologic Catchment Area study[66] the estimated 1-year prevalence was 5.0% for unipolar major depression and 5.4% for dysthymia. Estimates were 10.3% for major depressive episode and 2.5% for dysthymia in the National Comorbidity Survey.[67] However, the point prevalence rates for depression range from 18% to 30% after acute myocardial infarction,[68-70] and estimates are as high as 40% in persons with ischemic heart disease[6,20,21,34] versus about 5% in the general population.[66] In these cases, the taking of a β-blocker may be confounded with the association between depression and the disease state.

Few of these studies reported comorbidities. This point may be particularly important in elderly persons with multiple medical conditions. It is plausible that β-blockers have a significant association with depression in diseases with lesser psychological component (e.g., hypertension), but taking a β-blocker adds little to the depression associated with diseases having a major psychological component, such as myocardial infarction.

Misclassification Error and Selection Bias

Many studies assumed dispensing for an antidepressant was a proxy for depression, but this may not be the case. Indications for antidepressants other than for depression include enuresis, panic disorder, chronic pain, and migraine.[71] Consequently, patients classified as depressed on the basis of dispensing of an antidepressant may be misclassified.

Selection bias is an important aspect of study design. Examples of potential selection biases that may influence the findings include participants who were survivors of a cohort,[26] prior personal or family history of depression,[12,16,18,20,21,25,26,29,30] and duration of treatment. Observational studies may suffer from length bias or prevalence/incidence bias.[6,72,73] For example, successful treatment of clinical depression generally requires filling the prescription for an extended period of time, usually 6 months or longer. Classifying patients with single dispensings for antidepressants as depressed may result in misclassification.

Temporal Ordering and Time Frame

Another misclassification-related issue is that cross-sectional studies and studies using automated databases frequently do not distinguish the temporal ordering in the relationship between depression and β-blocker use or dispensing. Automated database studies generally do not report whether the drug was dispensed before or after the depression marker was measured. A few studies have tried to specify this relationship.[28-30,33] Bright and Everitt[30] created a variable to indicate whether the diagnosis was before or after the initial β-blocker dispensing and found no significant relationship. Two other studies[28,33] estimated the risk based on whether the β-blocker was prescribed first. One study[28] found that the overall prevalence of concurrent antidepressant use was higher in the β-blocker group and the other[33] found that depression occurred no more frequently in β-blocker users than in other members of the study base. Hallas[74] found that equal proportions of patients were dispensed antidepressants and β-blockers "first" in a Danish study.

Finally, a study[75] has shown that the wrong exposure window can under- or overestimate the relationship and that the choice of prescription time windows can influence the estimates of exposure risk. Bright and Everitt[30] examined different time windows of: (1) 7–90 days, (2) use during the prior year, and (3) "any history of use" in the one study that evaluated time windows. However, they found that the results for shorter time windows before the index date were of similar magnitude.

Comparison Group

An estimate of excess risk implies comparison with a control group. Selection of the control group has a significant impact on interpretation of the findings. In one study,[6] the comparison group was primarily patients prescribed calcium-channel blockers. A few case reports[43,76] have associated calcium-channel blockers with depression, although depression generally has not been attributed to these agents.[77] However, depressive-like adverse effects such as fatigue and listlessness are occasionally reported with calcium-channel blockers. In other studies,[25,29,35] patients receiving propranolol were compared with patients taking other drugs that are also reputed to be associated with depression. In interpreting these findings, does a lack of difference between β-blocker patients and control group patients mean that they are at no greater risk than the general population? Or does it mean that β-blocker users were

at no greater risk than controls who also are taking medications associated with high degrees of depression? This distinction is important in any evaluation of whether β-blockers are associated with depression.

Miscellaneous Issues

Several of the larger and more influential studies[18,28,30] have used dispensing of β-blockers as the measure of exposure. A question that constantly accompanies automated database studies is whether a dispensed prescription is the same as ingesting the drug.

Sociodemographic factors such as gender, living arrangements, health status, and medical utilization have been shown to be related to depression,[30,48] but few of the reviewed studies controlled for these factors. For example, controlling for benzodiazepine use, the number of other medications, and medical care utilization reduced a significant crude association to the null in one study.[30]

Discussion

IMPLICATIONS FOR FUTURE RESEARCH

The purposes of this review were to describe and critique the literature to guide future studies and to raise specific questions important to elucidate this relationship. The major policy question is whether β-blockers may be unjustly associated with depression and their use avoided for that reason. If so, persons who may have otherwise benefited may not realize the positive effects of the β-blockers.[78] The risk of depression with β-blocker use should be carefully examined in the future because many of the issues surrounding this question still are murky.

The first issue is whether the findings are associated with the quality of the study design. Most of the early evidence supporting an association between depression and β-blocker use was based on case reports and case series reports. Findings from cross-sectional, observational studies and case–control studies have been more equivocal. Randomized controlled and randomized double-blind trials are stronger study designs and provide less support for the association. However, they have other concerns that leave a finding of no association equivocal, especially a need for better case definitions and larger samples. Obviously, ethical questions would be raised if randomized controlled trials were designed for the sole purpose of investigating major depressive syndrome as the major end point. Consequently, rigorous measures of depression should be added to randomized controlled trials investigating the use of β-blockers for other therapeutic end points and safety, such as for myocardial infarction. These trials would help to address the issue of excess attributable risk.

There are other important reasons for conducting additional studies on this issue, including an evaluation of whether the relationship between β-blocker use and development of major depressive disorder is greater in subgroups of users. Subgroups that should be studied are those with prior or family history of major depressive disorder, people with serious medical conditions that are appropriately treated with β-blockers, and people taking β-blockers for less psychologically burdensome conditions such as hypertension. Clinicians need to know whether these risk factors put people at elevated risk of development of depression with the use of β-blockers. Is the attributable risk of depression due to β-blocker use when they already are at greater risk of depression because of their myocardial infarction? One could hypothesize that since these patients already are at such high risk for depression that β-blocker use would add little to their baseline risk. Conversely, people with diseases with low baseline risk for depression (e.g., hypertension, glaucoma) might find themselves put at unacceptably higher risk when they use β-blockers. Future studies need to assess whether the risk/benefit ratio of β-blockers is favorable when prescribed for diseases with a large psychological burden or, if it is unfavorable, whether β-blocker prescribing should be avoided or delayed.

The second issue is whether findings of an association are spurious and due to inappropriate case definition. Studies using a rigorous diagnosis of depression as an end point have not shown a relationship between β-blocker use and depression. Studies using depressive symptoms, standardized measures of depressive symptomatology, or antidepressant dispensings as a marker for depression are more equivocal regarding the association. Differences in case definition and measurement instruments could partially explain the inconsistency of the findings. No epidemiologic measure of depression and depressive symptomatology accurately reflects the gamut of depressive syndrome symptoms. Even so, future studies should use more than a single item about mood and strive to determine whether persons have clinical depression or severe depressive symptomatology based on accepted diagnostic and screening procedures. A worthwhile future endeavor would be to develop a gold standard measure of depression (or evaluate currently available measures more comprehensively) for use in pharmacoepidemiologic and other large-scale studies of depression in ambulatory populations.

It is also important to determine whether associations with certain measures of depressive symptomatology are largely a function of the measurement properties of the scales, or whether the mood change is in response to the chronic CNS adverse effects or a biochemical response to the β-blockers. Similarly, a worthwhile endeavor would be to distinguish the dimensions of depressive symptomatology scales that are most associated with β-blocker use, whether it is dysthymic mood, somatic/physiologic, or psychological. Such research would provide insight as to whether the association is a major depressive symptomatology or CNS-related lethargy and fatigue.

A related measurement issue is the sensitivity and specificity of different measures of depression and the effect of misclassification error. For example, even when the end point is depression diagnosis, there is still concern about accuracy of the diagnosis in primary care, ambulatory-based studies.[47,56] Case definitions of depression must be carefully described and applied and the inaccurate use of the word "depression" must be avoided in the future so that it is not misinterpreted or confused.

Future studies must use appropriate comparison groups to accurately weigh the risks and benefits of prescribing a β-blocker versus a medication from another therapeutic

category. First, an important issue in drawing conclusions about the relationship between depression and β-blocker use is the type of β-blocker. This issue has not been resolved because there is evidence both for and against the hypothesis that lipophilic β-blockers cause more frequent depression than do hydrophilic β-blockers. Future comparison groups should include persons taking medications that have not been shown to have a relationship with depression.

Finally, future studies should avoid altogether or adjust for risk factors and study design characteristics that may be confounded with diagnosis. Appropriate strategies such as stratification, matching, sample restriction, and standardization should be used.[79,80] The temporal ordering of the relationship must be clarified in each study, and appropriate exposure time windows should be explored.[75] From both scientific and clinical viewpoints, it is important to know whether newly identified depression in a person started on a β-blocker less than 1 month previously is more likely to have been caused by the β-blocker than newly identified depression in a person whose β-blocker treatment started more than 1 year ago.

SOCIAL AND ECONOMIC IMPLICATIONS

The social and economic implications of this issue are multifaceted and may be confounded by factors other than the drug. For example, studies using antidepressant dispensing as the outcome measure have been consistently associated with β-blocker use. Is it because patients dispensed antidepressants have more "depression," or is it because they are high users of other services and prescriptions? It is possible that they are "sicker" and at greater risk to take drugs in general, including β-blockers, so there is a higher but spurious association. It is possible that their depression is due to the disease rather than the β-blocker. What can be learned from patients taking β-blockers and antidepressants without a diagnosis of depression? Is it simply an undocumented diagnosis? Hypochondriasis? Is the antidepressant dispensing due to somatic diseases and their depression-like symptoms that physicians are just trying to ameliorate? Other confounding social factors associated with depression that should be studied include age, gender, functional status, and whether there is a previous personal history of depression or a family history of depression. Careful psychosocial investigations into this phenomenon are warranted.

There are economic implications in formulary drug treatment choices if β-blockers do cause depression or depressive symptoms. Decisions on alternative drug therapies should consider the additional cost of depression treatment for the segment of the population at risk. Even if the β-blockers rarely precipitate major depressive syndrome, there are implications for patients experiencing drug-related dysthymia, fatigue, listlessness, or other symptoms that are clearly related to the β-blockers. These symptoms certainly have significant implications for patient quality of life.[81]

Conclusions

The strength of the studies and their support for the association between β-blockers and depression is not scientifically persuasive. Sound scientific studies are needed to clear up the murky issues confounding the purported association to provide the information practitioners need to care for their patients.

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