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The Screening and Management of Comorbid Depression in Type 1 Diabetes for Improved Compliance

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By

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INTRODUCTION

Advanced practice and primary care providers are increasingly managing the ever-growing population of patients with diabetes—with a 2016 American Academy of Family Physicians (AAFP) study from the Medical Expenditures Panel Survey (MEPS) finding that a full 48 percent of medical encounters for the subset of patients with diabetes but no other chronic health conditions were in fact managed by general clinicians.[1] Patients with diabetes face chronic, severe sequelae of their disease, often suffering comorbid conditions as well, including mental health diagnoses. Physician assistants (PAs) are likely to face increased diabetic patient caseloads—frequently including patients with unmet mental healthcare needs, and a review of the current literature on management is warranted in order to optimize care.

Clinicians are typically familiar with the general course and management of the more prevalent type 2 diabetes. Type 1 diabetes, specifically, is an autoimmune condition typically diagnosed in childhood and which, unlike some forms and stages of type 2 diabetes, requires immediate and lifelong insulin therapy, with use of lancets, meters, and injections of insulin every few hours. Diet and exercise are first line preventative treatments for new onset type 2 diabetes, and oral medications can then be initiated to stall progression to insulin-dependent type 2 in general practice. Type 1 diabetics, however, typically do not have clinically actionable preventative therapeutic and lifestyle modification windows. Although autoimmune cascade-halting preventative drug target studies are promising,[2,3,4] they are currently in the nascent stages of development, and no current diet nor oral medication reliably prevents type 1 in humans. For these reasons, clinicians in both endocrinology specialties and in the primary care setting need data on best practice guidelines as well as to be apprised of known comorbidities

their patients are likely to face, from what is an unpreventable diagnosis in the case of type 1, and often a difficult to prevent diagnosis in type 2.

HIGH RATE OF DIABETIC KETOACIDOSIS IN YOUNG DIABETICS

Due to the nature of their autoimmune destruction of beta cells of Langerhans, type 1 diabetics are prone to rapid diabetic ketoacidosis (DKA) decompensation, especially with poor insulin management. Foster's 2019 management and outcomes comparison of type 1 registry patient characteristics from two cohorts between 2016-2018 and 2010-2012 shed light on the most common age range for DKA events requiring overnight hospitalization in that population, namely adolescents and young adults, and child patients with poor glycemic control and depression leads to more emergency room visits. Not without precedent, the study also found that between the ages of 15-18, patient metabolic control worsened to the point that average Hgba1c for that age group averaged 9.3% (78 mmol/mol). These patients were also at a heightened risk of experiencing ketoacidosis in the three months prior. This study's probands were found to have a marked risk of DKA in teenagers and young adults.[5,9] Tellingly, patients with higher average Hgba1c levels are at an increased risk for DKA ($P<0.001$). [5]

HIGH RATE OF CARDIOVASCULAR COMPLICATIONS IN TYPE 1

Complications of diabetes are frequent in both type 1 and type 2 diabetes – even in children and teens. A 2017 observational study by colleagues of the Colorado School of Public Health's Department of Epidemiology between 2002-2015 across-five sites of type 1 and type 2 diabetic patients diagnosed younger than age 20 found significant complications in even young patients. Type 1 patients were shown to have high rates of cardiovascular complications found by sphygmoCor-Vx pulse wave velocity, demonstrating arterial stiffness. The same patients also

exhibited heightened risk of blood pressures equal or greater to the 95th%ile by age (<18).

Further, patients had poor glucose control, as shown by an average Hgba1c of 9.2 (5.7%

normal).[6] Patients frequently struggle to maintain healthy glucose control, whether type 1 or

type 2, but type 1 patients do not have struggling pancreatic function to fall back on and can

almost immediately decompensate. Further care to optimize dosing is necessary for both sets

of patients.

COMORBIDITY OF DEPRESSED MOOD OR MAJOR DEPRESSIVE DISORDER (MDD) IN TYPE 1

A recent 2019 Danish clinic questionnaire combined with medical records analysis for

the purpose of evaluating quality of life, found complications of diabetes associated strongly

with depressed mood. The researchers used the status of ever having an upper limb soft tissue

diabetic lesion (using color photographs in case patients were unfamiliar with the medical

terminology for their dermopathy) and found higher risk of depressed mood (P<0.01) in that

subset. The WHO-Five Well-being Index (WHO-5) is a Danish-developed scale with greater

scores pointing toward best possible quality of life based on positive mood, restful sleep,

activity, and general interest in one's future. WHO-5 scores below or equal to 50 indicate a high

risk of stress or depression. In the questionnaire study, duration of diabetes, BMI, blood

pressure, HbA1c, urinary albumin to creatinine ratio (UACR), and vibration perception threshold

(VPT) were all measured, and quality of life WHO-5 scores in all patients with at least one such

lesion were significantly lower. This data demonstrates the mood burden of diabetic sequelae.[7]

Another commonly utilized option is the Beck Triad of Depression Inventory, assessing patient

beliefs about their own value, the fairness of the world, and the potential for the future to be

better than today. Clinicians will typically find most useful the metric developed by Drs. Spitzer,

Williams, and Kroenke's: Patient Health Questionnaire-9 (PHQ-9) or the abbreviated form of which (PHQ-2). PHQ-2 asks the patient to reflect on the last two weeks and to state if 1) they have had little interest or pleasure in doing things and 2) if they have found themselves feeling down, depressed, or hopeless.

A separate King's College of London 2017 study examining data from the 1958 British birth cohort of over 8000 subjects showed a bidirectional relationship between autoimmune disorder and depression. Importantly, the retrospective paper found this association held true independent of genetic risk of depression in these individuals. Likewise, depression was found to increase the subsequent hazard of developing an autoimmune disorder, (P = 0.0095). This may point to additive genetic risk previously unaccounted for in genome wide association studies (GWAS).[8,13,14,15] Common environmental exposures, baseline inflammation levels, and behaviors common to one which influence development of the other (e.g. depression leading to low exercise and vitamin D deficiency or diabetes leading to high inflammation, social withdrawal, etc) may explain the strong linkage as more data emerges. The 1958 data originally come from the cohort of all individuals born during one week in 1958 in Scotland, England, and Wales, using self-report data from age 33, age 42, and age 46, their genotype data of 2002-2004, from which polygenic risk scores for depression were generated for each individual. Due to the multiple collection points of the data over the years, the study was uniquely able to support a bidirectional relationship.[8] In addition to autoimmune comorbidity, studies have shown that the burden of poorly-controlled and mood-based compliance with regimen lead to adverse outcomes. History of diagnosed depression, diabetes-related distress, and depressed mood were associated with a higher rate of microvascular complications. Diagnosed depression and diabetes-related distress

also showed higher HbA1c at baseline when insulin was initiated. Insulin therapy improved glycemic control, while preexisting depressed mood declined and diabetes-related distress remained unchanged. [7, 10, 13, 14, 19]

TREATMENT MODALITIES: CONCOMITANT TALK THERAPY

Of the 21% of respondents in the 2019 Danish study who were diagnosed with depression, 52% had been given counseling therapy by primary care, 55% counseling with a psychiatrist, and 62% had been prescribed antidepressant medication. WHO-5 scores for this subgroup were also assessed, resulting in lower quality of life score. The patients in this survey were more likely (40% versus 16%) to score <50 on the WHO-5 if they had ever been diagnosed with depression (P<0.001). This Danish cohort who responded had better average glucose control than average diabetic patients, but unfortunately, rates of depression even in this self-responding, better-compliance group were two-to three-times higher among T1D patients than the general population, consistent with previous findings in the literature.[7]

TREATMENT MODALITIES: CHOICE OF SSRI (BLACK BOX WARNING FOR CHILDREN AND TEENS)

Various studies have examined the use of Selective Serotonin Reuptake Inhibitors SSRI and other antidepressant medications in the case of autoimmune disease and specifically diabetes. A 2012 study in northern India over the course of 12 months followed 40 adult patients in outpatient endocrinology with Hba1c >7% were assigned to SSRI treatment. Fasting, postprandial, and Hba1c%, and then all patients were maintained on their current diabetic medication while also being prescribed 10 mg/day of escitalopram, although without a sham study arm. Patients were maintained or increased on their dose until they achieved control of depression symptoms. This Gehlawat, et al. study found better glycemic control with the use of

SSRI, specifically escitalopram. Unfortunately, a les common HAM-D depression scoring system was used, so the results are not easily compared across studies. However, static dose and titrating dose arms of the study showed a significant difference in depression outcomes (p <0.001).[9] Similarly, an Alvar 2017 meta-analysis and guideline review for nurse practitioners utilized antidepressant fluoxetine, sertraline, or escitalopram to treat comorbid depression in diabetics.[10] The review recommended compliance with the American Academy of Pediatrics (AAP) suggestion of annual screening for depressive symptoms beginning at age 11, unless patients of their families present with worrisome symptoms or complains earlier. [10,9]

Previously, an older 2011 Markowitz, et al. metanalysis of depression treatment in diabetes and outcomes found mixed success and reporting methods of glycemic control in talk therapy—generally cognitive behavioral therapy (CBT)—and SSRI treated probands. One of the reviewed double-blind random controlled trails had a fairly robust cohort (n=351) of both type 1 and type 2 diabetics, and used sertraline intervention after Beck Depression Inventory (BDI), showing 42% of patients on the regimen achieved remission of depression symptoms.[11] Unfortunately, screening methodologies and outcome measures were not equivalent between the various studies, so comparisons across studies are currently difficult to substantiate. [11, 10]

Thought positive effects on mood and diabetic management have been found, clinicians must also consider the pharmacokinetics and pharmacodynamics of the SSRIs themselves. Common side effects of SSRIs include typical gastrointestinal complaints. In children and teenagers, there are black box warnings for volitional effects such as increased risk for suicidal ideation or attempt when initiating treatment, necessitating close follow up and stabilization. [10] Typically, SSRIs are dose dependent for sexual dysfunction (especially sertraline when

increasing 100 to 150). Fluoxetine, sertraline, and escitalopram are frequently used in studies

due to their relatively low side effects and length of time on the market. Citalopram may not be

an ideal antidepressant in this population as its use is correlated with excessive weight gain and

the AAFP and FDA have cautioned on its use in patients with risks for torsades de pointes,

though follow up studies have failed to replicate QT prolongation risk. Escitalopram has been

shown to cause fewer sexual side effects than other anti-depressants and may benefit patients

with intimacy concerns, especially as diabetics are a population with increased risk of erectile

dysfunction.[12, 16, 17, 18]

MEDICATION AND FOLLOW UP

Especially when treating minors, psychiatric referral, therapy referral, family support,

and good clinical follow up are vital. Weekly visits and close management are ideal. [10, 13, 16]

Drug. Lower age limit, starting dosage	Fluoxetine (>8 years old, initiate 5 mg anticipatory guidance GI upset and black box warning with return 1 month,	Sertraline (>6 years old, initiate 12.5 mg anticipatory guidance GI upset and black box warning with return 1 month,	Escitalopram (>12 years old, initiate 5 mg anticipatory guidance GI upset and black box warning with return 1 month,
Titration and Therapeutic Target Dosage	titrate by 5 mg, target dose 10-20 mg at least 12 months,	titrate by 25 mg, target dose 50-100 mg at least 12 months,	titrate by 5 mg, target dose 10-20 mg at least 12 months,

Maximum Dose and Cessation	max dose 40 mg, 2 months to taper off entire class)	max dose 200 mg, 2 months to taper off entire class),	max dose 20 mg, 2 months to taper off entire class)
Supportive studies	Alvar meta-analysis NP 2017 Lexi-Comp, inc Gehlawat 2013	Alvar meta-analysis NP 2017 Lexi-Comp, inc	Alvar meta-analysis NP 2017 Lexi-Comp, inc

CONCLUSION

In summation, the current literature points to the necessity and efficacy of primary care providers managing diabetic depression as a means of treating the whole person and though is corroborated generally by small sample sizes, shows great promise in both glucoregulation and improved quality of life. Gaps in the literature such as the plausibility of common autoimmune mechanism and long term outcomes of treatment would best be resolved by establishing larger cohorts of patients on talk therapy regimens or SSRI therapy in order to have larger, more generalizable groups to study, ideally with beneficial outcomes for individual patients. Clinicians still know little about long term SSRI effects in depressed diabetics. Also, the autoimmune cascade is understood, but causal or correlational mechanisms with mood have not been fully elicited. It will also be important to examine targeted treatments towards avolition (e.g. escitalopram) aspects of depression versus anhedonia (e.g. sertraline) targets. Further studies may also look at the ideal length of treatment and separate talk therapy from diabetes management skills training or study the two combined. Future studies on these parameters after the implementation of depression management in type 1 diabetes will present important clinical data for best practice.

In conclusion, PAs should prioritize SSRI, talk therapy, or preferably a combination of the two for all type 1 diabetic patients under their care until quality of life measures, depression screening goals, compliance, and Hgba1c levels are maintained. Caution must be taken with the initiation of all SSRIs, especially in minors, who must be followed closely as well as have a parent or guardian onboard for warning signs of rare though serious black box SSRI initiation outcomes in minors (i.e. increased goal-directed behavior in the context of suicidal ideation). [10] Drawbacks in application also include the necessity of managing potential tapering of medication or the transfer to psychiatric management.

SUMMARY OF ACTIONABLE OUTCOMES TABLE

SCREENING: PHQ-2 In the past 2 weeks, have you 1) had little interest or pleasure in doing things? and 2) felt down, depressed, or hopeless?
TREATMENT INITIATION: 1) Talk therapy initiation of weekly and then bimonthly meetings with a therapist 2) If age 12 or older, initiate escitalopram. If ages 6-12, initiate sertraline. In minors stress blackbox warning of suicidality potential and follow up immediately and frequently. Continue medications for a minimum of 12 months.
EVALUATION OF DIABETIC AND DEPRESSION OUTCOMES: Focus on patient experience, Hgba1c goals, quality of life WHO-5, re-evaluation of PHQ-2.
TAPERING OF DEPRESSION CARE OR TRANSFER TO OVERSIGHT BY PSYCH: Discuss with patient and/or parents the efficacy of outcomes and take 2 months minimum to taper off medications.

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