OFP

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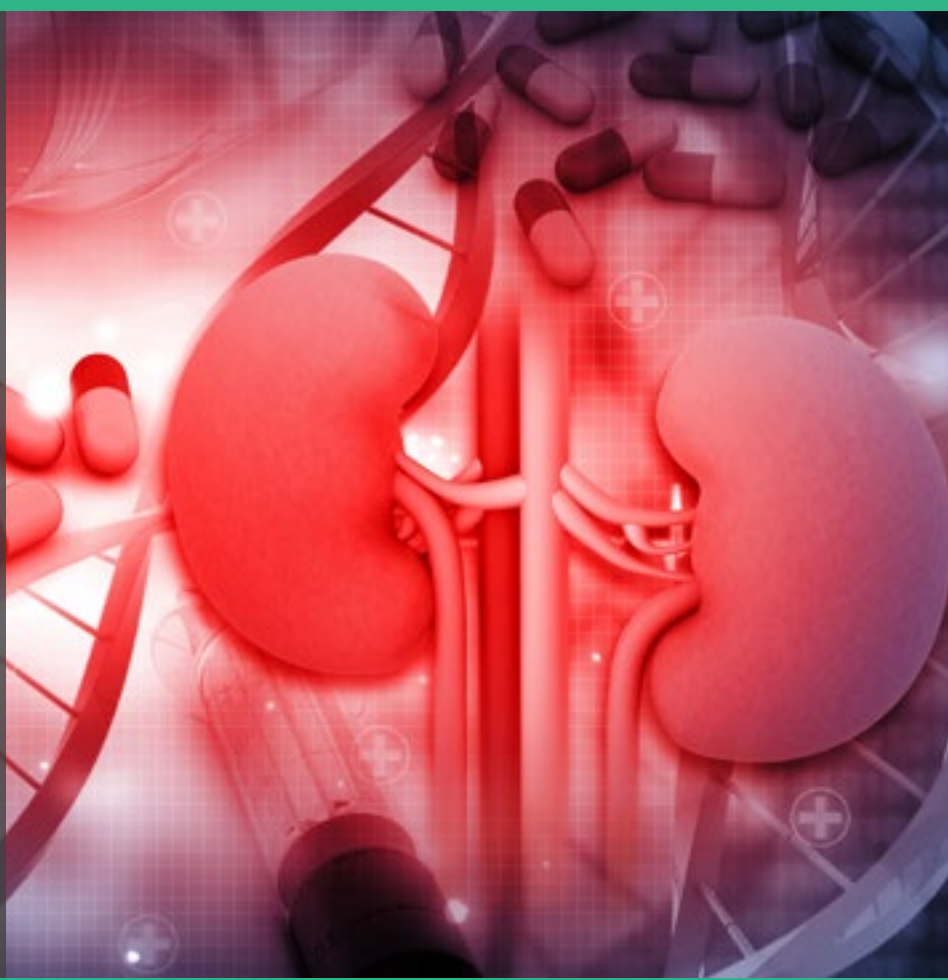

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PATIENT CARE SUMMARY

BLANCHARD, Floyd

908323323

DATE OF BIRTH
23-FEB-1948 (66 years)

GENDER
Male

ATTRIBUTED CLINICIAN
BLACKWELL, Elizabeth

GROUP
Able Clinic

LAST VISIT
BANTING, Frederick
21-AUG-2014 | 14:30

NEXT VISIT
BANTING, Frederick
24-NOV-2014 | 09:45

TOBACCO FREE
YES

INFLUENZA VACCINATION
YES

PNEUMOCOCCAL VACCINATION

CLINICAL NOTES

Last ER Visit: 29-OCT-2013
ER Diagnosis: Unstable Angina
Last Admission: 29-OCT-2013
Admission Diagnosis: NSTEMI
Specialist Type: NSTEMI
Specialist Name: N/A

Practice Coordinator:
Addressed Medications, Order Labs.

CHRONIC HEART FAILURE

ACEI	YES	20-SEP-2013 Draft
ARB		
Beta Blocker	YES	21-AUG-2014 Draft
Ejection Fraction	40%	21-AUG-2014 Draft
OSA Screening	YES	30-AUG-2014 Draft
Warfarin Anticoagulant	YES	20-SEP-2013 Draft

CORONARY ARTERY DISEASE

Aspirin	YES	21-AUG-2014 Draft
Beta Blocker	YES	20-SEP-2013 Draft
Low-density Lipoprotein Cholesterol	138	21-AUG-2014 Draft
Statin	YES	21-AUG-2014 Draft

DIABETES

Foot Exam	Medical Reason for not performing a Foot Exam	
Hemoglobin A1C	7.2	21-AUG-2014 Draft
Low-density Lipoprotein Cholesterol	138	21-AUG-2014 Draft
Microalbumin	YES	21-AUG-2014 Draft

ASTHMA

Spirometry	YES	01-DEC-2013 Draft
Longterm Control Medication		
Peak Flow	YES	20-SEP-2013 Draft
SABA	YES	21-AUG-2013 Draft

ADULT AND ADOLESCENT IMMUNIZATIONS

Tetanus, Diphtheria, Pertussis Vaccine (Td/Tdap)	YES	21-AUG-2014 Draft
Varicella Zoster Virus (VZV)	YES	14-AUG-2013 Draft

COLORECTAL CANCER SCREENING

Colonoscopy	YES	10-MAR-2008 Draft

BLOOD PRESSURE
160/105
21-AUG-2014 (Last Previous)

BMI
39
21-AUG-2014 (Data Pending)

HEIGHT
5' 10"
21-AUG-2014 Draft

WEIGHT
250 lbs
21-AUG-2014 Draft

eGFR
64 mL/min/1.73m²
21-AUG-2014 Draft

SERUM CREATININE
YES
21-AUG-2014 Draft

FASTING BLOOD GLUCOSE
142 mg/dL
21-AUG-2014 Draft

TOTAL CHOLESTEROL
200 mg/dL
21-AUG-2014 Data Entry

LDL 138 mg/dL
HDL 61

TRIGLYCERIDES
148 mg/dL

Symphony PERFORMANCE HEALTH

The information contained herein provides general information and does NOT provide comprehensive clinical findings or medical results for which medical treatment should be based. Any and all medical decisions or treatment plans should be developed by treating physician based solely upon his or her training, expertise and judgment.

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Date address changed
Complete
Outcome Out of Range
Patient Excluded
Incomplete or Data Not Old

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- Chronic Kidney Disease
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OFP

Osteopathic Family Physician

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IN THIS ISSUE

American Osteopathic Board of Family Physicans Exam Schedule

EXAM	DATES AND EXAM LOCATION	POSTMARK APPLICATION DEADLINE
Family Medicine/OMT Certification - Cognitive Exam	**Electronic Testing; Regional Sites** September 26, 2015	CLOSED
Family Medicine/OMT OCC/ Recertification - Cognitive Exam	**Electronic Testing; Regional Sites** September 26, 2015	CLOSED
Family Medicine/OMT Certfication Performance Evaluation ONLY	**AOA OMED Conference** October 17-21, 2015; Orlando, FL October 16-17, 2015	CLOSED
Family Medicine/OMT OCC/Recertfication Exam Performance Evaluation ONLY	**AOA OMED Conference** October 17-21, 2015; Orlando, FL October 17-18, 2015	CLOSED
Hospice & Palliative Medicine Conjoint CAQ Certification	**Orlando, FL** October 18, 2015	**June 1, 2015** filing with late fee July 1, 2015
Family Medicine/OMT Certification - Cognitive Exam	**Electronic Testing; Regional Sites** March 19, 2016	**October 1, 2015** filing with late fee thru December 1, 2015
Family Medicine/OMT Certfication Performance Evaluation ONLY	**ACOFP Conference** April 6-9, 2016; Puerto Rico April 4-8, 2016	**November 1, 2015** filing with late fee thru December 1, 2015
Family Medicine/OMT OCC/Recertfication Exam Performance Evaluation ONLY	**ACOFP Conference** April 6-9, 2016; Puerto Rico April 4-8, 2016	**November 1, 2015** filing with late fee thru December 1, 2015
Family Medicine/OMT Certfication Performance Evaluation ONLY	**ACOFP OMED Conference** September 16-20, 2016; Anaheim, CA September 16-18, 2016	**April 1, 2016** filing with late fee thru June 1, 2016
Family Medicine/OMT OCC/Recertfication Exam Performance Evaluation ONLY	**ACOFP OMED Conference** September 16-20, 2016; Anaheim, CA September 16-18, 2016	**April 1, 2016** filing with late fee thru June 1, 2016
Family Medicine/OMT Certfication - Cognitive Exam	**Electronic Testing; Regional Sites** September 24, 2016	**April 1, 2016** filing with late fee thru June 1, 2016
Family Medicine/OMT OCC/Recertfication - Cognitive Exam	**Electronic Testing; Regional Sites** September 24, 2016	**April 1, 2016** filing with late fee thru June 1, 2016

Dates may be subject to change. Visit the AOBFP website at www. aobfp.org for additional information on all exams and to download the appropriate application form, or call 847.640.8477.

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Clara Carls, DO, Procedures

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Katherine Clark, DO, FACOFP, Injections

Steven Clay, DO, Addiction

Randall Colucci, DO, Nutrition

Robert Danoff, DO, Emergency Medicine and Preventive Medicine

Robin Devine, DO, Statistics/Design

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Dennis Eckles, DO, Diabetes, Rural Medicine

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Editor's Message

Drugs, Mood, Sex and Skin, Articles for a Generalist

Amy J. Keenum, DO, PharmD, Editor, Osteopathic Family Physician

As a journal for osteopathic family physicians we seek to print articles related to common conditions or scenarios in general clinical practice rather than writings about rare exotic diseases. To that end, topics this month relate to the treatment of diabetes with a relatively new drug class, prescribing of statin medications, a skin condition related to summer and sun, mood disorders like depression, and sexual counseling in patients with cardiovascular disease.

A review of the use of Sodium Glucose Co-Transporter 2(SGLT2) Inhibitors in the treatment of diabetes and the role of renal function is a nice introduction to this group of medications. Their exact role in the treatment of diabetes remains to be seen. As with most new drugs, the initial studies compare the drugs to placebo but in reality patient outcomes are not compared to placebo but to what other available medicines do. Consideration of possible consequences of raising the urinary glucose content has to be part of the decision tree to prescribe these medicines as well as the need to consider estimated glomerular filtration rate (e-gfr).

The decision to prescribe statins or not to prescribe statins is made multiple times a day in the offices of osteopathic family physicians. The estimation of overall cardiovascular risk is key to deciding response to the lipid panels we order daily. Employer based insurance plans require patients in my region to have lipid panels drawn even though they are not indicated either by age or frequency. It is unlikely that these groups of patients are going to need statins if they have no comorbidities. Beyond that, the use of cardiovascular calculators are the standard of care in 2015 in patients who do not have diabetes, hypertension or known heart disease. The article in this issue uses several cases to illustrate key points to statin prescribing. This is an area where a well-designed electronic medical record could be helpful. It is a computer after all and calculations and lists are what computers do best.

Mood disorders are common in primary care and the article in this issue discusses the spectrum of mood disorders including dysthymia, unipolar and bipolar depression. It is a challenge to care for these conditions in a 15-minute appointment. As I find myself time challenged trying to cope with a first appointment with one or more of these conditions and I walk out of the room late for the rest of the day, it helps me better understand why psychiatrists and psychologists have longer initial booking times for psychiatric conditions.

Sexual counseling is fairly common in primary care and this issue includes an article on the topic of sexual counseling and cardiovascular disease. It outlines several assessment tools not handy in my office on a daily basis so the author is probably right that more training of primary care physicians is probably in order. The article talks about advising patients with angina, after a myocardial infarction, after bypass surgery, or ICD placement plus other conditions commonly seen in primary care when it is safe to have sex.

1877-5773X/$ - see front matter.

We are running a summer edition of common skin conditions with pictures. This month has a case of photodermatitis, which brings back memories of the time my family lived in South Florida and my father had a coworker who grew limes. The gentleman would bring to the office those that were too big to sell, and we made limeade by the gallon. One of my siblings developed a photodermatitis as a result. My parents were so impressed with the doctor's ability to diagnose this condition.

Let us know what you think of the dermatology section. We are trying to do a visual item like dermatology or radiology on a regular interval – of course depending on the quality of the submissions.

FROM THE PRESIDENT'S DESK

Single Accreditation System Progress

Kevin de Regnier, DO, FACOFP dist.
2015 ACOFP President

As I write this, the AOA House of Delegates has just concluded and the single accreditation system (SAS) was front and center.

As you may recall, the 2014 ACOFP Congress of Delegates expressed serious concerns about the impact a single GME accreditation system would have on our family medicine residencies and on the profession as a whole. These sentiments were conveyed to the AOA in 2014 ACOFP Resolution 13 which requested the AOA;

(to) withdraw from the MOU (memorandum of understanding between the AOA/AACOM & ACGME) by December 31, 2015 if any of the principles listed below that are considered to be non-negotiable items are not included in the MOU, or by an amendment to the MOU:

- *A requirement that all Graduate Medical Education (GME) programs recognize the Comprehensive Osteopathic Medical Licensure Examination of the United States (COMLEX-USA) results as equivalent to meet examination criteria for admission into the new consolidated and unified Graduate Medical Education (GME) programs,*
- *That graduates of Colleges of Osteopathic Medicine accredited by the AOA Commission on Osteopathic College Accreditation (COCA) will remain eligible for entry into all ACGME programs on an equal basis with U.S. and Canadian graduates of Colleges of Medicine accredited by the Liaison Committee on Medical Education (LCME) or the Committee on Accreditation of Canadian Medical Schools (CACMS),*
- *A requirement that if osteopathic physicians in the new unified GME accreditation programs take osteopathic board certification examinations, those osteopathic board certification examinations be recognized as equivalent to the American Board of Medical Specialties (ABMS) certification examinations and be counted equally with allopathic certification toward the required certification examination pass rate in the Basic Residency Standards.*
- *That the new unified GME accreditation programs recognize AOA Board Certification on an equal basis with ABMS certification for the positions of program director, director of medical education, and designated institutional officer without requiring an exception be granted by the applicable Residency Review Committee (RRC); ....* [1]

At the just completed AOA House of Delegates, ACGME CEO Tom Nasca, MD and AOA Trustee Boyd Buser, DO, FACOFP, reported on the progress that has been made toward resolving many, though not all of our concerns. They reported:

- The COMLEX exam will continue to be accepted for entry into ACGME programs
- ACGME created a pre-accreditation status for AOA programs applying for ACGME accreditation to allow residents unimpeded access to all ACGME residency and fellowship programs
- A new Osteopathic Neuromusculoskeletal Medicine Review Committee (RC) has been established and residency standards produced and approved
- A new Osteopathic Principles Committee has been established and standards have been produced and approved
- 20 of 24 review committees have announced that they will accept AOA certification for program directors, one committee has not yet met to discuss this issue
- Osteopathic representatives have been added to ACGME review committees for which there are AOA training programs
- Institutions began formal application processes on 4/1/2015
- Individual Programs began application process on 7/1/2015
- 29 institutions have applied for ACGME accreditation; six have been awarded initial accreditation
- Two AOA programs have submitted applications for ACGME accreditation
- A recent survey shows 83% of program directors are considering osteopathic recognition for their programs

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2015 ACOFP President Email: president@acofp.org

- Current ACGME programs have inquired about application to achieve osteopathic recognition
- ACGME has instructed RCs to develop language consistent with the expectation that DOs will take AOA certifying board examinations. [2]

As you can see, there has been great progress made in addressing many of the concerns raised by the ACOFP Congress of delegates.

But it hasn't just been the AOA, AACOM, and the ACGME doing all the work, the ACOFP has been doing its part to ensure a successful transition to the SAS. We have nominated and had three members appointed to the family medicine review committee. A member nominated by the ACOFP has been appointed to the osteopathic neuromusculoskeletal medicine RC and four ACOFP members serve on the osteopathic principals committee.

Additionally, the ACOFP has reviewed and submitted comments on proposed changes to the ACGME FM standards, the OPC standards, and the ONMM standards. On each occasion we joined with the AOA and or the American Academy of Osteopathy in submitting our comments.

The ACOFP will continue to monitor the progress of the development and implementation of the single accreditation system to ensure that the concerns raised by our Congress of Delegates are fully addressed and the profession is preserved.

REFERENCE

1. http://www.acofp.org/ACOFPIMIS/acofporg/PDFs/About/Past_Resolutions/2014/Res_13_AOA-AACOM_Unified_Residency_Accreditation_System.pdf, accessed July 23, 2015
2. http://www.osteopathic.org/inside-aoa/single-gme-accreditation-system/Pages/2015-HOD-single-gme-update.aspx accessed July 23, 2015

REVIEW ARTICLE

Sodium Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes Mellitus

Eden Miller, DO[1] and Jay H. Shubrook Jr, DO, FACOFP, FAAFP, BC-ADM[2]
[1]CEO, Diabetes Nation, High Lakes Health Care, Bend, OR
[2]Professor, Primary Care Department, Touro University California College of Osteopathic Medicine, Vallejo, CA

KEYWORDS:

Type 2 Diabetes Mellitus

Renal Glucose Reabsorption

SGLT2 Inhibitors

Efficacy

Safety

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease, control of which typically requires multiple therapies. Current guidelines suggest that, in addition to improving glycemic control, antihyperglycemic therapy should be chosen on the basis of its effects on body weight and the risk of hypoglycemia. The newest class of oral antihyperglycemic agents, the sodium glucose co-transporter 2 (SGLT2) inhibitors, reduces renal glucose reabsorption and increases urinary glucose excretion via an insulin-independent mechanism of action. SGLT2 inhibitors have been shown to improve glycemic control and to reduce body weight and systolic blood pressure, and their use is associated with a low risk of hypoglycemia. This paper explains the mechanism of action of SGLT2 inhibitors and reviews published efficacy and safety data from phase 3 clinical trials and pooled analyses for the three SGLT2 inhibitors currently approved by the U.S. Food and Drug Administration for use in patients with T2DM: canagliflozin (Invokana®), dapagliflozin (Farxiga™), and empagliflozin (Jardiance®). Implications for clinical osteopathic practice are discussed.

INTRODUCTION

The sodium glucose co-transporter 2 (SGLT2) inhibitors are the first agents to address hyperglycemia by targeting the kidneys in patients with type 2 diabetes mellitus (T2DM). Three medications in this therapeutic class entered the U.S. market within 17 months — canagliflozin in March 2013, followed by dapagliflozin in January 2014, and empagliflozin in August 2014.[1-3] SGLT2 inhibitors are included in the 2013 treatment algorithm of the American Association of Clinical Endocrinologists (AACE),[4] and in the 2015 American Diabetes Association (ADA) Standards of Medical Care.[5]

To offer guidance on the place of SGLT2 inhibitors in osteopathic clinical practice, this review describes the mechanism of action of these agents and summarizes efficacy and safety data from phase 3 clinical trials with the three SGLT2 inhibitors available in the United States.

ROLE OF THE KIDNEYS IN HYPERGLYCEMIA & DIABETES

The kidneys influence glucose homeostasis primarily by reabsorbing glucose from the glomerular filtrate. In healthy individuals, virtually all of the filtered glucose is reabsorbed into the circulation.[6] The majority of glucose reabsorption (about 90%) occurs through SGLT2, which is located almost exclusively in the proximal tubule.[6]

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When the plasma glucose concentration exceeds 180 - 200 mg/dL in healthy adults (the renal threshold),[7,8] the reabsorptive capacity of the kidneys is exceeded and glucose is excreted in the urine.[6] In patients with diabetes, the renal threshold for glucose is increased by as much as 20%, to up to 240 mg/dL.[8-10] This change is counterproductive because the hyper-reabsorption of glucose leads to maintenance or exacerbation of the hyperglycemic state, rather than spilling excess glucose into the urine.[6,11]

SGLT2 INHIBITORS

MECHANISM OF ACTION

Canagliflozin, dapagliflozin, and empagliflozin are all highly selective inhibitors of SGLT2.[12-15] Inhibition of SGLT2 reduces renal glucose reabsorption and lowers the renal threshold for glucose reabsorption, leading to increased urinary glucose excretion (UGE) and reduction of hyperglycemia in patients with T2DM.[12,16] UGE attributable to SGLT2 inhibition is approximately 80-120 g/day with canagliflozin 100 mg and 300 mg,[17-20] approximately 70 g/day with dapagliflozin 10 mg,[21] and approximately 78 g/day with empagliflozin 25 mg.[22] In addition, canagliflozin 300mg has been shown to lower postprandial glucose excursion, likely because local concentrations of canagliflozin in the gut lumen may be sufficient to transiently inhibit intestinal SGLT1.[23-25] As SGLT2 inhibitors act independently of beta-cell function or insulin sensitivity,[26] this class of medication can be used in all stages of diabetes.[27,28]

Small studies have reported an increase in endogenous glucose production (EGP) with SGLT2 inhibitors;[23, 29, 30] plasma glucose showed a net decrease despite elevated EGP. The mechanism of this phenomenon is currently unexplained, but elevated EGP may be a compensatory response to support normal plasma glucose levels in the presence of sustained UGE.[23]

CLINICAL BENEFITS

A systematic review and meta-analysis of clinical trials comparing SGLT2 inhibitors with placebo (45 studies, n=11,232) or active comparator (13 studies, n=5,175) reported improved glycemic control, reduced body mass, and reduced blood pressure with SGLT2 inhibitor therapy.[31] These effects have been confirmed by other published reviews.[32-34] Although glycated hemoglobin A (A1C) improved in all groups of patients, those with higher baseline A1C values generally experienced greater A1C reductions.[30, 35-37]

SAFETY

Side effects associated with the SGLT2 inhibitor class and its mechanism of action of increasing UGE include genital mycotic infections (GMIs), urinary tract infections (UTIs), osmotic diuresis-related events, and volume depletion.[32] When SGLT2 inhibitors are used as monotherapy, the risk of hypoglycemia is comparable to that of other classes of antihyperglycemic agents (AHA) that are not associated with hypoglycemia.[31, 36] Rates of serious adverse events (AEs) range between 1.0% and 12.6%, and AEs resulting in discontinuation of therapy range between 0.9% and 9.9%.[32]

Glycemic lowering by SGLT2 inhibitors depends on glomerular filtration; therefore, efficacy may be reduced in patients with renal impairment. The prescribing information for each SGLT2 inhibitor includes recommendations specific to patients with reduced renal function. Patients with estimated glomerular filtration rate (eGFR) ≥ 45 to < 60 mL/min/1.73 m^2 should receive only lower-dose canagliflozin (100 mg), whereas empagliflozin 10 mg and 25 mg can be used in patients with eGFR ≥ 45 mL/min/1.73 m^2.[17, 22] Dapagliflozin is not indicated in this patient population.[21] Canagliflozin and empagliflozin should not be initiated in individuals with an eGFR < 45 mL/min/1.73 m2.[17, 22] Dapagliflozin should not be started in patients with eGFR < 60 mL/min/1.73 m^2.[21] Renal function should be monitored and SGLT2 therapy discontinued if eGFR remains persistently below these levels (eGFR: < 45 mL/min/1.73 m^2 for canagliflozin and empagliflozin, and < 60 mL/min/1.73 m^2 for dapagliflozin).[17, 21, 22]

EFFICACY AND SAFETY OF INDIVIDUAL U.S. FOOD AND DRUG ADMINISTRATION–APPROVED AGENTS

CANAGLIFLOZIN: EFFICACY AND CLINICAL BENEFITS

Table 1 *(pages 12-17)* summarizes the results of phase 3 trials of canagliflozin.[35, 36, 38-44] Compared with placebo, canagliflozin 100 mg and 300 mg significantly reduced A1C from baseline to 26 weeks when given as monotherapy, dual therapy (added to metformin), or triple therapy (added to metformin plus a sulfonylurea or metformin plus pioglitazone).[35, 36, 40, 42]

When compared with glimepiride[38] or sitagliptin[40] as add-on therapy to metformin for 52 weeks, A1C reduction with canagliflozin 300 mg was superior to that of comparators, whereas A1C reduction with canagliflozin 100 mg was non-inferior to comparators. In a study comparing canagliflozin 300 mg with sitagliptin as add-on therapy to metformin plus a sulfonylurea, canagliflozin 300 mg produced A1C reduction superior to that of sitagliptin.[41]

As monotherapy, dual therapy (added to metformin), and triple therapy (added to metformin plus a sulfonylurea), canagliflozin 100 mg and 300 mg were associated with significantly greater reductions in body weight at 26 weeks compared with placebo.[35, 36, 40] As dual therapy (added to metformin), canagliflozin at both doses was associated with significantly greater body weight reduction versus sitagliptin[40] or glimepiride at 52 weeks.[38] As triple therapy (added to metformin plus a sulfonylurea), canagliflozin 300 mg was associated with significantly greater body weight reduction than sitagliptin at 52 weeks.[41] Weight reduction early in canagliflozin treatment is likely, in part, attributable to fluid loss;[45] however, over time, the reduction in body weight is mainly attributable to reduction in fat mass.[38]

Compared with placebo, canagliflozin 100 mg and 300 mg significantly reduced systolic blood pressure (SBP) as monotherapy and as dual therapy (added to metformin) at 26 weeks,[35, 40] and as dual therapy (added to metformin)[40] and triple therapy (added tor metformin plus a sulfonylurea)[41] compared with sitagliptin at 52 weeks. As dual therapy (added to metformin), canagliflozin modestly reduced SBP at 52 weeks compared with glimepiride, which was associated with a small increase.[38] As triple therapy (added to metformin plus a sulfonylurea), canagliflozin was associated with numerical SBP reductions at 26 weeks.[36]

High-density lipoprotein cholesterol (HDL-C) significantly increased with canagliflozin 100 mg and 300 mg at 26 weeks as monotherapy[35] and triple therapy,[42] compared with placebo. In other studies, changes in HDL-C with canagliflozin were either

TABLE 1:

Efficacy and Safety of CANA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]			
		A1C (%)	Body Weight (kg)	SBP (mmHg)	HDL-C (%)
Monotherapy					
Stenlöf et al. 2013[35]	CANA 100mg (n=195)	−0.77[b]	−2.5[b]	−3.3 (0.8)[b]	11.2 (1.4)[b]
	CANA 300mg (n=197)	−1.03[b]	−3.4[b]	−5.0 (0.8)[b]	10.6 (1.4)[c]
	PBO (n=192) **26 weeks**	0.14	−0.5	0.4 (0.8)	4.5 (1.4)
Combination Therapy					
Cefalu et al. 2013[38]	**MET + one of:** CANA 100mg (n=483)	−0.82 (0.04)[d]	−3.7 (0.2)[f]	−3.3 (0.6)	7.9 (0.8)
	CANA 300mg (n=485)	−0.93 (0.04)[e]	−4.0 (0.2)[f]	−4.6 (0.6)	9.0 (0.8)
	GLIM (n=482) **52 weeks**	−0.81 (0.04)	0.7 (0.2)	0.2 (0.6)	0.3 (0.8)
Leiter et al. 2014[39]	**MET + one of:** CANA 100mg (n=483)	−0.65	−3.6	−2.0	9.4
	CANA 300mg (n=485)	−0.74	−3.6	−3.1	10.0
	GLIM (n=482) **104 weeks**	−0.55	0.8	1.7	0.7
Lavalle-González et al. 2013[40]	**MET + one of:** CANA 100mg (n=368)	−0.73 (0.05)[d]	−3.3 (0.2)[g]	−3.5 (0.6)[g]	11.2 (1.0)
	CANA 300mg (n=367)	−0.88 (0.05)[e]	−3.7 (0.2)[g]	−4.7 (0.6)[g]	13.2 (1.1)
	SITA (n=366) **52 weeks**	−0.73 (0.05)	−1.2 (0.2)	−0.7 (0.6)	6.0 (1.1)
Schernthaner et al. 2013[41]	**MET + SU + one of:** CANA 300mg (n=377)	−1.03[e]	−2.3[g]	−5.1[g]	7.6
	SITA (n=378) **52 weeks**	−0.66	0.1	−0.9	0.6

Safety					
GMIs (%)	**UTIs (%)**	**↑ Urinary Frequency (%)**	**↑ Urinary Volume (%)**	**Postural Dizziness (%)**	**Orthostatic Hypotension (%)**
Monotherapy					
2.5 M, 8.8 F	7.2	2.6	0	0.5	0
5.6 M, 7.4 F	5.1	3.0	3.0	1.0	1.0
0 M, 3.8 F	4.2	0.5	0	0	0
Combination Therapy					
7 M, 11 F	6	3	<1	<1	<1
8 M, 14 F	6	3	<1	<1	<1
1 M, 2 F	5	<1	<1	<1	0
9.5 M, 13.9 F	10.6	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
9.1 M, 15. 6 F	8.7				
1.9 M, 2.7 F	6.8				
5.2 M, 11.3 F	7.90	5.7	0.5	0.5	0
2.4 M, 9.9 F	4.90	3.0	0.5	0.5	0.3
1.2 M, 2.6 F	6.30	0.5	0	0.3	0
9.2 M, 15.3 F	4.00	1.6	0.8	0	0
0.5 M, 4.3 F	5.60	1.3	0	0.5	0.3

TABLE 1 (CON'T):

Efficacy and Safety of CANA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]			
		A1C (%)	Body Weight (kg)	SBP (mmHg)	HDL-C (%)
Combination Therapy (Continued)					
Wilding et al. 2013[36,h]	**MET + SU + one of:** CANA 100mg (n=157)	−0.74	−2.0	−3.7 (1.0)	6.6 (1.3)
	CANA 300mg (n=156)	−0.96	−3.1	−2.9 (1.0)	8.2 (1.3)
	PBO (n=156) **52 weeks**	0.01	−1.0	0.1 (1.0)	3.3 (1.3)
Forst et al. 2014[42] (26-week core period)	**MET + PIO + one of:** CANA 100mg (n=113)	−0.89[b]	−2.6[b]	−5.3 (1.0)[c]	7.2 (1.4)[i]
	CANA 300mg (n=114)	−1.03[b]	−3.7[b]	−4.7 (1.0)[i]	8.9 (1.3)[b]
	PBO (n=115) **26 weeks**	−0.26	−0.2	−1.2 (1.0)	2.4 (1.4)
Forst et al. 2014[42] (full trial period)[h]	CANA 100mg (n=113)	−0.92	−2.5	−3.4 (1.1)	7.0 (1.6)
	CANA 300mg (n=114)	−1.03	−3.6	−3.7 (1.1)	11.4 (1.6)
	PBO/SITA (n=115) **52 weeks**	NR	NR	NR	NR
Special Populations					
Bode et al. 2013[43] (patients aged 55-80 years)	**Current treatment + one of:** CANA 100mg (n=241)	−0.60[b]	−2.2[b]	−3.5 (1.0)[b]	6.8 (1.2)[b]
	CANA 300mg (n=236)	−0.73[b]	−2.8[b]	−6.8 (1.1)[b]	6.2 (1.2)[b]
	PBO (n=237) **26 weeks**	−0.03	−0.1	1.1 (1.0)	1.5 (1.2)

Safety					
GMIs (%)	**UTIs (%)**	**↑ Urinary Frequency (%)**	**↑ Urinary Volume (%)**	**Postural Dizziness (%)**	**Orthostatic Hypotension (%)**
Combination Therapy (Continued)					
7.9 M, 18.5 F	8.3	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
5.7 M, 18.8 F	8.3				
1.3 M, 5.0 F	7.7				
Safety data reported only at 52 weeks					
3.9 M, 16.7 F	5.3	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
4.8 M, 21.6 F	7.9				
0 M, 7.7 F	7.8				
Special Populations					
3.2 M, 15.4 F	5.8	2.5	1.7	0.8	0.8
6.2 M, 11.2 F	8.1	5.1	1.7	1.3	0.4
0 M, 2.1 F	5.1	2.1	0	0.4	0

TABLE 1 (CON'T):

Efficacy and Safety of CANA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]			
		A1C (%)	Body Weight (kg)	SBP (mmHg)	HDL-C (%)
Special Populations (Continued)					
Yale et al. 2013[44] (patients with CKD)	CANA 100mg (n=90)	−0.33[j]	−1.2	−6.1 (1.5)	4.0 (1.7)
	CANA 300mg (n=89)	−0.44[b]	−1.4	−6.4 (1.5)	3.0 (1.8)
	PBO (n=90) **26 weeks**	−0.03	0.2	−0.3 (1.5)	1.5 (1.8)

[a] Least-squares mean change from baseline value (with standard error in parentheses where provided).
[b] p<0.001 vs. PBO, difference vs. baseline.
[c] p<0.01 vs. comparator or PBO, difference vs. baseline.
[d] Non-inferior to comparator.
[e] Superior to comparator.
[f] p<0.0001 vs. comparator, difference vs. baseline.
[g] p<0.001 vs. comparator, difference vs. baseline.

(CONTINUED)

*EFFICACY AND CLINICAL BENEFITS - **CANAGLIFLOZIN***

In older adults (aged 55-80 years), canagliflozin 100mg and 300mg as add-on therapy to study participants' current treatment regimens was associated with significant reductions from baseline in A1C, body weight, and SBP, and an increase in HDL-C relative to placebo.[43] The A1C reduction in older adults (aged ≥ 65 years) was numerically smaller than in younger patients (aged < 65 years).[47] It is suggested that reduced renal function in patients aged ≥ 65 years may explain this finding because A1C reductions were comparable between older and younger patients when controlling for eGFR.[47]

Canagliflozin (100mg and 300mg) significantly reduced A1C compared with placebo in adults with T2DM and Stage 3 chronic kidney disease (CKD; eGFR ≥ 30 to < 50mL/min/173 m^2) (Table 1).[44] Numerical changes in body weight, SBP, and HDL-C favored canagliflozin, but statistical comparisons were not performed. Analysis of pooled data from four randomized, placebo-controlled phase 3 studies showed statistically significant reductions in A1C with canagliflozin 100mg and 300mg in patients with Stage 3a (eGFR ≥ 45 to < 60mL/min/173 m^2) and 3b (eGFR ≥ 30 to < 45mL/min/173 m^2) CKD.[48]

CANAGLIFLOZIN: SAFETY

Safety results of phase 3 trials of canagliflozin are summarized in Table 1 *(pages 12-17)*. In a pooled analysis of four phase 3 trials, the most commonly reported AEs deemed related to canagliflozin are GMIs and UTIs.[46]

GMIs were reported in 3.2% of women with placebo and in 10.4% and 11.4% with canagliflozin 100mg and 300mg, respectively.[46] GMIs also occurred in men receiving canagliflozin, although less often than in women (0.6% with placebo vs. 4.2% and 3.7% with canagliflozin 100mg and 300mg, respectively).[46] In both men and women, GMIs were mild or moderate in intensity and resolved with standard antifungal therapy.[46]

Canagliflozin therapy resulted in a slight increase in UTIs relative to placebo (4.0% with placebo vs. 5.9% and 4.3% with canagliflozin 100mg and 300mg, respectively), with low rates of serious UTIs and no increased incidence in upper UTIs.[46] AEs associated with osmotic diuresis (0.8% with placebo vs. 6.7% and 5.6% with canagliflozin 100mg and 300mg, respectively) and volume depletion (1.1% with placebo vs. 1.2% and 1.3% with canagliflozin 100mg and 300mg, respectively) were also reported.[46]

Safety					
GMIs (%)	**UTIs (%)**	**↑ Urinary Frequency (%)**	**↑ Urinary Volume (%)**	**Postural Dizziness (%)**	**Orthostatic Hypotension (%)**
Special Populations (Continued)					
1.7 M, 3.1 F	5.6	2.2	0	1.10	0
2.1 M, 2.4 F	7.9	4.5	0	2.20	1.1
0 M, 0 F	5.6	1.1	0	0	0

[h] Statistical analysis not performed.
[i] p<0.025 vs. PBO.
[j] p<0.05 vs. PBO, difference vs. baseline.

A1C, glycated hemoglobin A_{1c}; CANA, canagliflozin; CKD, chronic kidney disease; F, females; GLIM, glimepiride; GMIs, genital mycotic infections; HDL-C, high-density lipoprotein cholesterol; M, males; MET, metformin; NR, not recorded; PBO, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SITA, sitagliptin; SU, sulfonylurea; UTIs, urinary tract infections.

The occurrence of serious AEs was similar across treatment groups (< 4%), and treatment discontinuation was low overall with no discernible relation to dose (3.1% in the placebo group vs. 4.3% and 3.6% with canagliflozin 100mg and 300mg, respectively).[46]

The incidence of hypoglycemia was similar between canagliflozin monotherapy and placebo when patients were not on background therapy, including a sulfonylurea (2.2% with placebo vs. 3.8% and 4.3% with canagliflozin 100mg and 300mg, respectively). However, it occurs more frequently, as expected, with canagliflozin dual therapy (with a sulfonylurea) relative to placebo (15.4% with placebo vs. 27.4% and 30.1% with canagliflozin 100mg and 300mg, respectively). This is consistent with the pattern seen when an AHA with a low risk of hypoglycemia is given to patients on an AHA with a high risk of hypoglycemia (e.g. sulfonylurea, insulin).[46]

DAPAGLIFLOZIN: EFFICACY AND CLINICAL BENEFITS

Table 2 *(pages 18-21)* summarizes results of phase 3 trials of dapagliflozin.[30, 49-56] Compared with placebo, dapagliflozin 5mg and 10mg significantly reduced A1C as monotherapy,[30] and as dual therapy (added to metformin, glimepiride, pioglitazone, or insulin therapy).[50, 52-54] As triple therapy (added to metformin plus a sulfonylurea), dapagliflozin 10mg resulted in significantly greater A1C reduction relative to placebo; dapagliflozin 5mg was not evaluated.[55] As dual therapy (added to metformin), dapagliflozin (mean dose 9.2mg) compared with glipizide (mean dose 16.4mg) was statistically non-inferior in A1C reduction.[51]

Body weight changes with dapagliflozin monotherapy (5mg or 10mg) did not differ significantly from those observed with placebo after 24 weeks.[30] An extension of this study, comparing dapagliflozin 10mg monotherapy with placebo plus low-dose metformin therapy (with metformin added to placebo after 24 weeks) did show a significant difference in body weight change at 102 weeks.[49] Adding dapagliflozin 5mg or 10mg to metformin, glimepiride, pioglitazone, or insulin therapy resulted in significantly greater body weight reduction from baseline compared with placebo.[50, 52-54] A 24-week study of dapagliflozin concluded that the weight loss observed (difference from placebo in change from baseline: 2.1kg) was due to decreases in fat mass, visceral adipose tissue, and subcutaneous adipose tissue. Reduction in fat mass (rather than lean body mass) accounted for two-thirds of the weight loss.[57]

TABLE 2:

Efficacy and Safety of DAPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]			
		A1C (%)	Body Weight (kg)	SBP[b] (mmHg)	HDL-C (%)
Monotherapy					
Ferrannini et al. 2010[30] (main cohort only)	DAPA 5mg (n=64)	−0.77 (0.11)[c]	−2.8 (0.5)	−2.3 (1.9)	NR by treatment arm
	DAPA 10mg (n=70)	−0.89 (0.11)[d]	−3.2 (0.5)	−3.6 (1.9)	
	PBO (n=75) **24 weeks**	−0.23 (0.10)	−2.2 (0.4)	−0.9 (1.8)	
Combination Therapy					
Bailey et al. 2014[49]	DAPA 5mg (n=64)	−0.70	−1.59	1.9	NR
	DAPA 10mg (n=70)	−0.61	−3.94	3.9	NR
	PBO + low-dose MET (n=75) **102 weeks**	−0.17	−1.34	2.1	NR
Bailey et al. 2013[50]	**MET + one of:** DAPA 5mg (n=137)	−0.58[d]	−1.70[d]	−1.1 (13.2)[e]	NR
	DAPA 10mg (n=135)	−0.78[d]	−1.74[d]	−0.3 (15.0)[f]	NR
	PBO (n=137) **102 weeks**	0.02	1.36	1.5 (13.7)	NR
Nauck et al. 2011[51] (dose titration)	**MET + one of:** DAPA (n=406)	−0.52[g]	−3.22[d]	−4.3	5.88
	Glipizide (n=408) **52 weeks**	−0.52	1.44	0.8	−0.16
Strojek et al. 2011[52]	**GLIM + one of:** DAPA 5mg (n=142)	−0.63[d]	−1.56[h]	−4.0	4.49
	DAPA 10mg (n=151)	−0.82[d]	−2.26[d]	−5.0	5.21
	PBO (n=145) **24 weeks**	−0.13	−0.72	−1.2	2.37

Safety			
Events Suggestive of GMIs (%)	**Events Suggestive of UTIs (%)**	**Renal Impairment or Failure (%)**	**Hypotension, Dehydration, or Hypovolemia (%)**
Monotherapy			
7.8	12.5	NR	NR
12.9	5.7	NR	NR
1.3	4.0	NR	NR
Combination Therapy			
9.4	12.5	0	0
15.7	8.6	4.3	1.4
1.3	4.0	0	1.3
5.8 M, 23.5 F	8.8	2.9	2.2
6.5 M, 20.7 F	13.3	1.5	1.5
0 M, 11.5 F	8.0	1.5	1.5
5.3 M, 21.1 F	10.8	5.9	1.5
0.4 M, 5.4 F	6.4	3.4	0.7
2.8 M, 9.6 F	6.9	0.7	0
6.1 M, 7.1 F	5.3	0	0.7
0 M, 1.3 F	6.2	1.4	0

TABLE 2 (CON'T.):

Efficacy and Safety of DAPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]			
		A1C (%)	Body Weight (kg)	SBP[b] (mmHg)	HDL-C (%)
Combination Therapy (Continued)					
Rosenstock et al. 2012[53]	**PIO + one of:** DAPA 5mg (n=141)	−0.82 (0.08)[i]	0.09 (0.28)[d]	−0.8 (1.2)	NR by treatment arm
	DAPA 10mg (n=140)	−0.97 (0.08)[d]	−0.14 (0.28)[d]	−3.4 (1.2)	
	PBO (n=139) **24 weeks**	−0.42 (0.08)	1.64 (0.28)	1.3 (1.2)	
Wilding et al. 2012[54]	**INS + one of:** DAPA 5mg (n=211)	−0.96[c]	−1.00[c]	−4.33	NR
	DAPA 10mg (n=194)	−1.01[c]	−1.61[c]	−4.09	NR
	PBO (n=193) **48 weeks**	−0.47	0.82	−1.49	NR
Matthaei et al. 2013[55]	**MET + SU + one of:** DAPA 10mg (n=108)	−0.86[d]	−2.65[d]	−4.04[j]	NR
	PBO (n=108) **24 weeks**	−0.17	−0.58	−0.27	NR
Special Populations					
Kohan et al. 2013[56] (patients with moderate renal impairment)	DAPA 5mg (n=83)	−1.21	−0.24	−0.25 (9.5)	NR
	DAPA 10mg (n=85)	−0.75	−1.10	−2.51 (16.3)	NR
	PBO (n=84) **104 weeks**	−0.67	2.63	4.14 (14.1)	NR

[a] Adjusted mean change from baseline value (with standard error in parentheses where provided).
[b] Seated SBP.
[c] p<0.001 vs. comparator, difference vs. baseline.
[d] p<0.0001 vs. PBO or comparator, difference vs. baseline.
[e] p=0.0136 vs. PBO, difference vs. baseline.
[f] p=0.0067 vs. PBO, difference vs. baseline.
[g] Non-inferiority established.
[h] p=0.0091 vs. PBO.
[i] p=0.0007 vs. PBO.
[j] p=0.025 vs. PBO.

Safety			
Events Suggestive of GMIs (%)	**Events Suggestive of UTIs (%)**	**Renal Impairment or Failure (%)**	**Hypotension, Dehydration, or Hypovolemia (%)**
Combination Therapy (Continued)			
9.2	8.5	NR	NR
8.6	5.0	NR	NR
2.9	7.9	NR	NR
2.0 M, 17.0 F	10.8	2.8	2.4
9.1 M, 12.0 F	10.2	2.0	1.5
0 M, 5.1 F	5.1	1.5	1.0
5.5	6.4	NR	NR
0	6.4	NR	NR
Special Populations			
9.6	13.3	2.4	9.6
8.2	14.1	9.4	12.9
3.6	14.3	7.1	6.0

A1C, glycated hemoglobin A_{1c} ; DAPA, dapagliflozin; F, females; GLIM, glimepiride; GMIs, genital mycotic infections; HDL-C, high-density lipoprotein cholesterol; INS, insulin; M, males; MET, metformin; NR, not reported; PBO, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SU, sulfonylurea; UTIs, urinary tract infections.

(Continued from page 11)

*EFFICACY AND CLINICAL BENEFITS - **DAPAGLIFOZIN***

Significantly greater SBP reductions from baseline have been reported with dapagliflozin than with metformin alone[50] or metformin plus a sulfonylurea.[55] A separate study reported a non-significant increase in SBP with dapagliflozin 10mg compared with placebo plus low-dose metformin, which may have been due to the fact that this study population had a relatively normal SBP at baseline.[49] Although changes in HDL-C have not been reported by treatment arm in most of the dapagliflozin phase 3 trials, an analysis of pooled data from four phase 3 studies reported consistent increases in HDL-C with dapagliflozin.[58] Dapagliflozin has been associated with small increases in LDL-C (mean percentage change from baseline at week 24 ranged from 0.6% to 2.7% with dapagliflozin 2.5 mg, 5 mg, and 10 mg vs. −1.9% with placebo).[59]

Lowering of A1C with dapagliflozin 5 mg and 10 mg in T2DM patients with moderate renal impairment did not differ significantly from placebo at 24 weeks.[56]

DAPAGLIFLOZIN: SAFETY

Safety results of phase 3 trials of dapagliflozin are summarized in Table 2 *(pages 18-21)*. Separate analyses of pooled data have evaluated the incidence of GMIs and UTIs in 12 randomized, placebo-controlled, phase 2b/3 trials of dapagliflozin (n=4,545).[60, 61] These analyses included patients who had received placebo or dapagliflozin as monotherapy or as add-on therapy to metformin, insulin, a sulfonylurea, or a thiazolidinedione for 12-24 weeks. The incidence of diagnosed GMIs in women was 1.5% with placebo, and 8.4% and 6.9% with dapagliflozin 5mg and 10mg, respectively. In men, the incidence of GMIs was 0.1% with placebo, and 1.2% and 1.2% with dapagliflozin 5 mg and 10 mg, respectively. The incidence of diagnosed UTIs was 3.7% with placebo, and 5.7% and 4.3% with dapagliflozin 5 mg and 10 mg, respectively.[61] GMIs and UTIs were generally mild to moderate in severity and responded to conventional therapy.[59]

Various terms have been used to report hypotension in dapagliflozin trials; in some, hypotension is combined with hypovolemia and dehydration. In at least one trial, no incidents of orthostatic hypotension were reported.[53] Other studies have reported either no change from baseline in the proportion of patients experiencing orthostatic hypotension[51] or few hypotensive events across treatment groups.[30] A safety summary of dapagliflozin reported incidences of 0.6% and 0.8% for dapagliflozin 5 mg and 10mg, respectively, vs. 0.4% in the placebo group for events defined as volume depletion (hypotension, dehydration, and hypovolemia).[59] Of note, there is currently no data available on volume depletion-related AEs with dapagliflozin in patients with high cardiovascular risk. Patients using loop diuretics, those with eGFR < 60 mL/min/1.73 m^2, or those aged ≥ 65 years are at increased risk of these AEs.[62] Dapagliflozin trials did not address urinary frequency or urinary volume as AEs.

Use of dapagliflozin infrequently resulted in hypoglycemia; however, when used in combination with glimepiride[52] or insulin,[63] hypoglycemia incidence was increased compared with placebo.[64]

EMPAGLIFLOZIN: EFFICACY AND CLINICAL BENEFITS

Table 3 *(pages 24-27)* summarizes results of phase 3 trials of empagliflozin.[37, 65-70] A1C reduction with empagliflozin 10 mg or 25 mg was statistically superior to that observed with placebo when given as monotherapy[37] and in combination with metformin,[66] metformin plus a sulfonylurea,[65] pioglitazone, or pioglitazone plus metformin,[68] or multi-dose insulin with or without metformin.[69] As add-on therapy to metformin, empagliflozin 25 mg has been shown to be statistically superior to glimepiride (mean maximum titrated dose 2.71 mg/day) in a 104-week study.[67] A1C reduction with empagliflozin 10 mg and 25 mg was similar to A1C reduction with sitagliptin 100 mg.[37]

Statistically significant reductions in body weight and SBP (relative to placebo) have been observed with empagliflozin 10 mg and 25 mg as monotherapy,[37] in combination with metformin,[66] with metformin plus a sulfonylurea,[65] and with pioglitazone or pioglitazone plus metformin.[68] Empagliflozin 10 mg and 25 mg added to multi-dose insulin with or without metformin resulted in a statistically significant reduction in body weight and a non-significant reduction in SBP.[69] In combination with metformin, empagliflozin 25 mg resulted in statistically significant reductions in body weight and SBP compared with glimepiride.[67]

Empagliflozin added to metformin plus pioglitazone has been associated with small increases in HDL-C in placebo-controlled studies: 0.06 mmol/L (2.32 mg/dL) with empagliflozin 10 mg and 0.03 mmol/L (1.16 mg/dL) with empagliflozin 25 mg.[68] With metformin only, increases in HDL-C of 0.08 mmol/L (3.09 mg/dL) and 0.06 mmol/L (2.32 mg/dL) with empagliflozin 10 mg and 25 mg, respectively, relative to placebo were observed.[66] Empagliflozin as add-on to metformin has been reported to result in small increases in LDL-C (adjusted mean increase 0.15 mmol/L [5.80 mg/dL] with each dose) relative to placebo (0.03 mmol/L [1.16 mg/dL]).[66]

Empagliflozin 25 mg resulted in an adjusted mean change in A1C from baseline of –0.42% relative to placebo at week 24 in patients with eGFR ≥ 30 to < 60 mL/min/1.73 m^2.[70] In patients with Stage 2 and Stage 3 CKD, empagliflozin resulted in significant reductions in A1C, body weight, and SBP compared with placebo after 52 weeks, while in patients with Stage 4 CKD, numerical reductions in body weight and SBP were noted.[70]

EMPAGLIFLOZIN: SAFETY

Safety results of phase 3 trials of empagliflozin are summarized in Table 3 *(pages 24-27)*. Based on pooled analyses, the most frequently occurring AEs with empagliflozin are UTIs (7.6% with placebo vs. 9.3% and 7.6% with empagliflozin 10 mg and 25 mg, respectively) and GMIs (in female patients: 1.5% with placebo vs. 5.4% and 6.4% with empagliflozin 10 mg and 25 mg, respectively).[22] AEs related to osmotic diuresis and volume depletion have been evaluated from pooled data from phase 1, 2, and 3 studies in > 11,000 patients.[71] In that analysis, the overall incidence of volume depletion events was 1.4% with empagliflozin 10mg and 1.5% with empagliflozin 25 mg vs. 1.4% with placebo. The incidence of these events was higher in patients aged ≥ 75 years, those with eGFR < 30 mL/min/1.73m^2, and those also receiving diuretic therapy.[71] Empagliflozin therapy is associated with hypoglycemia when used with another AHA that has a high risk of hypoglycemia.[65,68,69]

IMPLICATIONS FOR PRACTICE

The successful management of patients with T2DM requires holistic care, addressing measures beyond A1C reduction. The ADA/European Association for the Study of Diabetes and the AACE recommend considering the impact on body weight and risk of hypoglycemia, as well as tolerability and cost, when selecting second- and third-line treatment regimens.[4, 5, 72]

Patient types that might be considered particularly good candidates for SGLT2 inhibitor therapy include overweight or obese individuals and those with high levels of insulin resistance or low levels of pancreatic beta-cell function. Clinicians may wish to exercise caution before prescribing SGLT2 inhibitor therapy for those with risk factors for volume depletion-related AEs and who also face elevated risk for falling or injury due to falls (e.g. osteoporosis, Parkinson disease, dementia).

SGLT2 inhibitors offer a novel mechanism of glycemic control by reducing renal glucose reabsorption and increasing UGE. Use of SGLT2 inhibitors offers the additional benefits of reducing blood pressure and body weight, with a low risk of hypoglycemia. The three SGLT2 inhibitors available in the United States, canagliflozin, dapagliflozin, and empagliflozin, are oral once-daily medications that improve glycemic control with a convenient dosing schedule. The most common side-effects are GMIs, UTIs, and increased urination. GMIs and UTIs are generally mild to moderate in severity, respond well to conventional treatment, and rarely result in treatment discontinuation. Studies are ongoing to provide further information on the long-term efficacy and safety of SGLT2 inhibitors and data will become available in the coming years. As SGLT2 inhibitors offer an insulin-independent mode of action, they can be used in patients at all stages of type 2 diabetes.[26-28]

TABLE 3:

Efficacy and Safety of EMPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]		
		A1C (%)	Body Weight (kg)	SBP (mmHg)
Monotherapy				
Roden et al. 2013[37]	EMPA 10mg (n=224)	−0.66[b]	−2.26[b]	−2.9[c]
	EMPA 25mg (n=87)	−0.78[b]	−2.48[b]	−3.7[d]
	PBO (n=228) **24 weeks**	0.08	−0.33	−0.3
Combination Therapy				
Häring et al. 2013[65]	**MET + SU + one of:** EMPA 10mg (n=225)	−0.82 (0.05)[e]	−2.16[e]	−4.1[f]
	EMPA 25mg (n=216)	−0.77 (0.05)[e]	−2.39[e]	−3.5[g]
	PBO (n=225) **24 weeks**	−0.17 (0.05)	−0.39	−1.4
Häring et al. 2014[66]	**MET + one of:** EMPA 10mg (n=217)	−0.70[e]	−2.08[e]	−4.5[e]
	EMPA 25mg (n=213)	−0.77[e]	−2.46[e]	−5.2[e]
	PBO (n=207) **24 weeks**	−0.13	−0.45	−0.4
Ridderstråle et al. 2014[67]	**MET + one of:** EMPA 25mg (n=765)	−0.66[h]	−3.1[b]	−3.1[b]
	GLIM 1-4mg (n=780) **104 weeks**	−0.55	1.3	2.5
Kovacs et al. 2013[68]	**PIO ± MET + one of:** EMPA 10mg (n=165)	−0.59 (0.07)[e]	−1.62 (0.21)[e]	−3.14 (0.9)[e]
	EMPA 25mg (n=168)	−0.72 (0.07)[e]	−1.47 (0.21)[e]	−4.00 (0.8)[e]
	PBO (n=165) **24 weeks**	−0.11 (0.07)	0.34 (0.21)	0.72 (0.9)

Safety		
UTIs (%)	**Events Consistent with GMIs (%)**	**Events Consistent with UTIs (%)**
Monotherapy		
6	3 M, 4 F	2 M, 15 F
4	1 M, 9 F	1 M, 13 F
4	0 M, 0 F	2 M, 9 F
Combination Therapy		
9.4	0.9 M, 4.5 F	2.7 M, 18.0 F
6.9	0.9 M, 3.9 F	0 M, 17.5 F
6.7	0.9 M, 0.9 F	2.7 M, 13.3 F
5.1	0.8 M, 7.6 F	0 M, 12.0 F
5.6	0.8 M, 9.7 F	0.8 M, 11.8 F
4.9	0 M, 0 F	2.6 M, 7.7 F
14	9 M, 15 F	7 M, 22 F
13	1 M, 3 F	5 M, 23 F
14.5	7.2 M, 9.8 F	3.6 M, 30.5 F
10.7	1.2 M, 6.0 F	2.4 M, 21.7 F
10.9	1.4 M, 3.3 F	8.2 M, 22.8 F

TABLE 3 (CON'T.):

Efficacy and Safety of EMPA in Randomized, Double-Blind Phase 3 Trials of Patients With Type 2 Diabetes Mellitus

Ref.	Regimen & Duration	Efficacy[a]		
		A1C (%)	Body Weight (kg)	SBP (mmHg)
Combination Therapy (Continued)				
Rosenstock et al. 2014[69]	**MDI INS ± MET + one of:** EMPA 10mg (n=186)	−1.18 (0.08)[e]	−1.95 (0.36)[e]	−3.4 (0.8)
	EMPA 25mg (n=189)	−1.27 (0.08)[e]	−2.04 (0.36)[e]	−3.8 (1.0)
	PBO (n=188) **52 weeks**	−0.81 (0.08)	0.44 (0.36)	−2.9 (1.0)
Special Populations				
Barnett et al. 2014[70] (patients with **Stage 2** CKD)	**Existing treatment + one of:** EMPA 10mg (n=98)	−0.57[b]	−2.00[i]	−1.7
	EMPA 25mg (n=97)	−0.60[b]	−2.60[b]	−6.2[b]
	PBO (n=95) **52 weeks**	0.06	−0.44	1.6
Barnett et al. 2014[70] (patients with **Stage 3** CKD)	**Existing treatment + one of:** EMPA 25mg (n=187)	−0.32[b]	−1.17[b]	−5.1[j]
	PBO (n=187) **52 weeks**	0.12	0.00	−0.8
Barnett et al. 2014[70] (patients with **Stage 4** CKD)	**Existing treatment + one of:** EMPA 25mg (n=37)	0.11 (1.48)	−1.0 (3.3)	−11.2 (15.7)
	PBO (n=37) **52 weeks**	−0.37 (0.79)	0 (3.6)	1.0 (17.4)

[a] Adjusted mean change from baseline value (with standard error in parentheses where provided).
[b] p<0.0001 for difference vs. PBO or comparator.
[c] p=0.0231 for difference vs. PBO.
[d] p=0.0028 for difference vs. PBO.
[e] p≤0.001 for difference vs. PBO.
[f] p=0.005 for difference vs. PBO.
[g] p=0.032 for difference vs. PBO.
[h] p=0.0153 (superiority) vs. GLIM.
[i] p=0.0006 for difference vs. PBO.
[j] p=0.0023 for difference vs. PBO.

Safety		
UTIs (%)	**Events Consistent with GMIs (%)**	**Events Consistent with UTIs (%)**
Combination Therapy (Continued)		
12.9	1.0 M, 7.9 F	5.2 M, 27.0 F
12.7	8.3 M, 10.5 F	3.6 M, 24.8 F
12.2	1.3 M, 1.8 F	0 M, 25.7 F
Special Populations		
14.3	10.0 M, 2.6 F	8.3 M, 23.7 F
9.3	0 M, 13.9 F	3.3 M, 19.4 F
15.8	3.6 M, 10.3 F	8.9 M, 25.6 F
16.6	1.9 M, 3.8 F	5.6 M, 31.3 F
15.5	0.9 M, 1.2 F	3.8 M, 30.9 F
18.9	0 M, 6.3 F	9.5 M, 31.3 F
8.1	0 M, 0 F	0 M, 16.7 F

A1C, glycated hemoglobin A_{1c}; CKD, chronic kidney disease; EMPA, empagliflozin; F, females; GLIM, glimepiride; GMIs, genital mycotic infections; INS, insulin; M, males; MDI, multiple daily injections; MET, metformin; open-label; PBO, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SU, sulfonylurea; UTIs, urinary tract infections.

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REVIEW ARTICLE

Guidelines for Sexual Counseling in Patients with Cardiovascular Disease

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Sexual intimacy has been considered to be an important element in determining the quality of life. Cardiovascular diseases (CVD) often attribute to many sexual disorders that may have a lasting impact on both the quality of life and functioning of both the patient and their partners. Due to its sensitive nature, the topic might not always be discussed after a cardiac event but patients do report asking for counseling specific to their cardiovascular disease. Various factors may serve, as obstacles to a proper sexual counseling so regular assessment for sexual dysfunction must be assessed in such patients. This articles aim to list out the various aspects of the sexual counseling physicians must consider while counseling his patients. Moreover, disease specific guidelines must also be explained to these patients as they may potentially lower the long-term morbidity.

INTRODUCTION

Sexual intimacy is an important factor in determining the quality of life in individuals. Its effects can be easily noticed in patients developing sexual dysfunctions post cardiovascular events. Even though patients report wanting information regarding sexual activity after such events, various factors (the sensitive nature of the topic, lack of the doctor's training in this topic, patients current condition being too ill and added anxiety to patient) serve as obstacles for this information flow from their healthcare providers.[1-4] The importance of overcoming such barriers have been emphasized by Steinke et al in a recent article published from the American Heart Association.[5] In this review we list out the most important disease specific points, which needs to be remembered while counseling such patients.

ASSESSMENT

Before proceeding with the sexual counseling, it is essential for the physician to assess the patient's current condition and willingness to discuss the topic. The concerns regarding sexual activity after a cardiac event are often not adequately voiced even though some patients do report asking for specific information.[1, 6, 7] As a result, routine assessment of the patients for such concerns is truly the most effective way of detecting and addressing the problem. Because of its sensitive nature, the method of counseling varies in different cultures and services.[8-11] Steinke et al reports that since these problems last a while, patients need to be counseled and followed up through a number of appointments.[5] This way a thorough assessment can be done along with providing a continuous guidance to the patient.[5] More importantly, the concerns in many of these patients are more than just physical so the physicians must also consider the psychological aspect while counseling. A cardiac event has been quite extensively correlated with psychological issues such fear[12-14] anxiety[15-17] and depression,[16, 18, 19] so it is important that psychological support must be carefully provided.

There have been two established methods that may be used by physicians to assess and provide the necessary sexual counseling. They are summarized in Table 1 (*page 32*). The PLISSIT method has been used for more than 35 years for clinical practice and research. However, some may argue that it is outdated and BETTER acronym might be a more appropriate approach to addressing the sexual concerns with the patient 20 Moreover, specific enquires related to the condition of the patients must be addressed to provide a more individualized counseling. In order to optimize these counseling sessions, assessment tools such as Index of Erectile Function-5 (ILEF-5),[21] Brief Male Sexual Function Inventory (BMSFI),[22] Brief Index of Sexual Functioning for Women (BISF-W),[23] Female Sexual Function Index (FSFI),[24] Arizona Sexual Experience Scale (ASEX),[25] Changes in Sexual

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TABLE 1:

Comparison between PLISSIT and BETTER method of assessment in sexual counseling

P.L.I.S.S.I.T	B.E.T.T.E.R
Permission – patient/partner is passively allowed to bring up the topic of sexuality and open up to the physician **L**imited **I**nformation – once patient/partner bring up the topic, provide general but limited information to them **S**pecific **S**uggestions- if further specific query is made by the patient/partner, then provide more information about it **I**ntensive **T**herapy – further counseling done by sex therapist or counselor or by the physician if he has the training for it.	**B**ring up the topic of sexuality, **E**xplain concerns you have about the patient's quality of life that may be impacted by their cardiac disease/event, **T**ell patients you can help guide them to resources that can address their concerns, **T**iming – assure the patient that these topics may be discussed in the future **E**ducate patients about the potential effects of their cardiac disease/event/treatments on their sexual functioning, **R**ecord or document the assessment and interventions provided

Functioning Questionnaire (CSFQ) and Changes in Sexual Functioning- Short Form (CSFQ-SF)[26, 27] may be utilized by the healthcare providers. Steinke et al have briefly summarized these assessment tools in the consensus article published by American Heart Association.[5]

GENERAL RECOMMENDATIONS FOR SEXUAL COUNSELING

Sexual counseling lead by a healthcare provider, to both the patient and their partners is generally helpful in aiding them to return to their sexual habits. The forms of assistance can be not only in form of appointment based counseling but also by information pamphlets or videos.[8, 28, 29] It is also necessary to remember that in addition to counseling the patient, the partners needs must also be addressed simultaneously[30-32] Since part of the counseling comprises a thorough assessment, healthcare professionals who are involved in such counseling must be trained to take focused history. These providers must also be equipped with the appropriate communications skills so they can provide the most appropriate and relevant data to the patient and their partners. Not to mention the need for individualized counseling geared towards their specific problem.[6, 8, 33, 34]

In general, healthcare providers must keep the following points in mind when counseling the patient and their partners:

- Evaluate the patient first to determine the readiness for him/her to resume sexual activity and advice them according to their current condition. If deemed low risk, the patient may be encouraged to become sexually active. However, if the patients condition poses a major threat to his/her health then they must be advised to withhold any sexual activity till his/her condition stable or has been properly managed.[5,28]

- If the patient's current condition is not deemed stable, (e.g. Patients with compromised heart function) then the couples should be encouraged to resort to activities which require less energy such as hugging, kissing or fondling instead of engaging in sexual intercourse. The patients must receive the appropriate treatments and their conditions must be stabilized before the resumption of sexual activity.[5, 28, 35, 36]

- Patients should be made aware of the possible symptoms that may appear during sexual activity and must be encouraged to report any of the symptoms to the physician. These symptoms can range from chest pain, shortness of breath, palpitations, and dizziness to insomnia or fatigue after sexual activity.[37-40]

- If the patient experiences chest pain during sexual activity then they may be prescribed nitroglycerine for use during or before intercourse.[39] However, if the chest pain persists beyond the scope of intercourse, they must be encouraged to contact the healthcare providers immediately.

- Patients must be advised to assume sexual positions, which are most comfortable for them.[41] Steinke et al has elaborated the various sexual position which may benefit for patients with chronic illness or stroke in the consensus document published by the American Heart Association.[5]

- Patients are encouraged to have sex in a familiar surrounding and with the usual partner as they have shown to be less stressful to the heart compared to a setting that is unfamiliar or in a secretive relationship.[37, 42, 43]

- If the patients condition permits, he/she should be encouraged to exercise regularly as that is associated with reduced risk for experience any cardiovascular accidents.[28]

- It is essential for the health care providers to have an idea about the medications the patient is currently on as some medications may be responsible for sexual dysfunction[7] (beta-blockers and diuretics may be responsible for erectile dysfunction, decreased libido, impaired ejaculation)[28, 44] The patients must also be made aware of these possible side effects. They should be encouraged to report the side effects of these medications immediately and also not to stop the medications just because they are facing these problems. The medications may be altered only if the change does not compromise the beneficial effects on the heart.

Disease specific guidelines that may be useful when counseling patients of cardiovascular diseases include:

Recommendations for Coronary Artery Disease, Angina, and Myocardial Infarction (MI):

- In an uncomplicated MI where the patients do not elicit any cardiac symptoms on mild to moderate activity, they may resume sexual activity after a week of the incident.[5, 28]

- After an MI, patients must be encouraged to gradually proceed with the sexual activity starting from activities, which require less stress on the body such as foreplay before engaging in an intercourse. As a result, the patient may have a greater understanding of their tolerance to sexual activity 5

- While counseling, patients must be reassured that < 5% of angina attacks are from sexual activity and it is less likely to occur to individuals who do not suffer form angina due to physical exercise. However, if the angina does persist beyond 15 minutes or beyond 5 minutes after nitrate use, they should be advised to contact the emergency services immediately.[45]

- As Phosphodiesterase type 5 (PDE5) inhibitors are contraindicated with nitrates, patients using PDE5 inhibitors before sexual activity must be warned of the potential adverse effects of using these medications together. If coital angina does appear during sexual activity in patients using PDE5 inhibitors, they should be advised to contact the emergency services immediately instead of using a nitrates.[46, 47]

Recommendations for CABG, cardic transplantation, and left ventricular assist device:

- Sexual activity in many patients may be disrupted after a CABG surgery due to poor self-image, preoperative functional impairments or from partner's anxiety or fears.[48-51] This problem can often be tackled by a having a detailed counseling session emphasizing on the instructions, which allow them to resume their normal sexual activity.[52-54] Patients must also be encouraged to participate in cardiac rehabilitation and therapy as they have proven to improve the sexual activity and satisfaction.[55-57]

- If the surgery was uncomplicated and depending on the degree of post-operative recovery, patients may resume sexual activity after 6 to 8 weeks after a standard CABG surgery.[28]

- Patients may resume sexual activity after placement of a left ventricular assist device (LVAD) as long as they have been given counseling sessions discussing the hooking up of the batteries, sexual position changes to accommodate the device and use of binders or barriers to protect the LVAD.[58,59]

- Cardiac rehabilitation in patients with heart transplant has shown to be useful in increasing their exercise capacity which in turn may play a pivotal role in improving their sexual performance.[60-63]

Recommendations for Heart Failure (HF) patients:

- Patients with compensated or mild HF (New York Heart Association class I or II) may be able to engage in sexual activity so the topic may be discussed during their routine visits to their healthcare provider.[28]

- During the counseling sessions the patients must be advised to engage in sexually activity only after their conditions have been optimally managed and stabilized.[28]

- Heart Failure patients must be advised to have a better understand their tolerance for sexual activity. Some general strategies such as taking rest before engaging or coital positions which are less stressful may be advised to ensure their sexual practices are more suited to their conditions.[41]

- Patients with decompensated or advanced (New York Heart Association class III or IV) Heart Failure must be advised not to take part in sexual activities until their condition is stabilized and/or optimally managed.[2]8

Recommendations after ICD Implantation:

- Sexual activity may be advised after an ICD is implanted, and it is generally safe for those who had the ICD implanted for preventive measures.[28]

- Sexual counseling in these patients must encompass certain factors such as the right time to resume sex, the potential for an ICD shock with intercourse, what to do if a shock occurs with sex, that an ICD shock will not harm the partner, the level of sexual activity that is safe and pregnancy counseling for women who wish to become pregnant.[13, 41, 64]

Recommendations for Congenital Heart Disease (CHD):

- Sexual activity is advisable for most patients with congenital heart disease (CHD), although those with decompensated or advanced Heart failure or history of previous cardiac accidents may need further evaluation and counseling before engaging in any form of sexual activity.[28]

- The sexual counseling of CHD patients comprise of psychological manifestations such as fear and anxiety, body image and self-esteem, contraception and pregnancy planning. Severity of the CHD may play a pivotal role in causing such manifestations, which in turn affect the sexual performance.[65, 66]

Recommendations after stroke:

- Recommendation for stroke patients is dependent on their current condition and proper assessment of their current physical condition must be done before any advise can be given.[67]

- All stroke survivors and their partners should be inquired about their sexual activity on a regular basis to ensure appropriate guidance.[67]

- Sexual activity may be advisable for patients after stroke but consideration to the concerns and difficulties must be addressed for both the patient and the partner. They must be made aware of the current condition and limitations to avoid provoking unnecessary stress and anxiety.[69]

- Patients may have to adopt new coital positions to ensure low stress during the sexual activity so they must be educated about the various coital position which allow the least possible physical stress on the patient's body.[5, 68]

CONCLUSION

Sexual health is an important determinant for a person's quality of life. The sexual counseling after a patient suffers a cardiac accident is often considered a sensitive topic; nonetheless it is a very important aspect, which should be kept in mind by the healthcare providers. Several studies mentioned in this article highlight the potential benefits of sexual counseling in such patient population. Patients must also be made aware of the resources available to them, including online resources (as listed out by Steinke et al).[7] Also more attention must be paid to make sure the healthcare professionals receive more training so patients receive more general as well as specific guidance relevant to their conditions. The use of PLISSIT or BETTER method may also enable the patients to convey their problems more readily to their physician. If developed and practiced correctly, sexual counseling not only has the potential to benefit patients greatly to return to their normal sexual activity but also help them improve their overall quality of life in the long run.

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REVIEW ARTICLE

Update on the Role of Statins in the Prevention of Atherosclerotic Cardiovascular Disease

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The treatment of dyslipidemia is evolving. New guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) and National Lipid Association (NLA) have brought changes to the previous standards of care. The ACC/AHA update no longer suggests treating to specific cholesterol goals, a new atherosclerotic cardiovascular disease assessment has been recommended, and treatment recommendations are divided into four statin benefit groups. The ACC/AHA focuses their update on lipid lowering therapy shown in clinical trials to provide long term cardiovascular risk reduction. The ACC/AHA and NLA guidelines are in agreement with statins as the chosen primary treatment but NLA guidelines continue to recommend treatment to specific LDL-C goals and stratify atherosclerotic cardiovascular disease (ASCVD) risk by number of risk factors and other conditions. The four statin treatment groups advised by the ACC/AHA update are patients with ASCVD, patients with primary elevation of LDL-C ≥ 190 mg/dL, patients with diabetes ages 40 to 75 years with LDL-C 70 to 189mg/dL, and patients without ASCVD or diabetes with an estimated 10-year ASCVD risk ≥ 7.5%. Due to the lack of clinical trial data in certain populations, the ACC/AHA guidelines outline fewer recommendations for younger patients, debate statin intensity choice in patients with diabetes, and provide less support for statin use in elderly patients. ASCVD risk should be evaluated in all adult patients. Risks and benefits of treatment should be considered with respect to patient preferences regarding therapy.

INTRODUCTION

As heart disease and stroke remain leading causes of death in the United States, there is a continued focus on improving the treatment of dyslipidemia as a major risk factor.[1,2] An update to the previous National Heart, Lung, and Blood Institute (NHLBI) lipid guidelines (National Cholesterol Education Program Adult Treatment Panel III) published in 2002 and updated in 2004 had been anticipated in 2013.[3,4] In place of these guidelines, the American College of Cardiology (ACC) and the American Heart Association (AHA) collaborated with the NHLBI to publish guidance documents for the assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults.[5] The ACC/AHA guidelines focus on the prevention of atherosclerotic cardiovascular disease (ASCVD) and are not intended as a comprehensive treatment strategy for dyslipidemia.[5]

The National Lipid Association (NLA) followed the ACC/AHA with a recent publication of guidelines addressing cholesterol screening and classification in adults, ASCVD risk assessment and treatment goals, and drug therapies intended to reduce morbidity and mortality.[6] The second part of the report is currently in development and will address lifestyle recommendations, groups with special considerations, patient adherence strategies, and team-based collaborative care. The NLA guidelines are intended to represent a comprehensive patient care approach that is similar to that provided by the prior NHLBI-sponsored guidelines.[6]

There are several notable changes to the treatment recommendations in the ACC/AHA guidelines. The updates no longer suggest treating to specific cholesterol goals, and instead utilize drug therapies that provide lipid lowering shown in clinical trials to provide long term cardiovascular risk reduction.[5] The use of a new ASCVD risk assessment tool is the basis for treatment recommendations.[7] The estimated 10-year ASCVD risk is defined as first occurrence of non-fatal myocardial infarction (MI), coronary heart disease (CHD) death, and nonfatal and fatal stroke.

Assessment of ASCVD risk should occur every 4 to 6 years for patients ages 20 to 79.[5,7] It is easily calculated using sex-specific pooled cohort equations found at www.myamericanheart.org/cvriskcalculator.[8] For patients ages 20 to 39 or those at low 10-year risk, ages 40 to 59, a long-term or lifetime risk calculation is recommended.[7] This long-term risk can be easily calculated by using the Framingham Heart cardiovascular risk calculator

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found at www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php.[6] These equations are well calibrated for non-Hispanic Whites and African Americans. They may overestimate ASCVD risk in American Indians and Asian Americans.[7] The ACC/AHA calculation also includes stroke risk where the Framingham does not. The NHLBI evidence grade for using the pooled cohort equations as the 10-year ASCVD risk calculator is E (expert opinion).[5] There has been much discussion regarding the accuracy of the ASCVD risk assessment tool.[9] Validation of efficacy has been published in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study in 2014.[10]

The treatment recommendations are divided into four "statin-benefit" groups based upon evidence from randomized controlled trials and meta-analyses published through July, 2013 (see Table 1).[5] Statin-based therapy is promoted as the primary pharmacotherapy choice, as clinical trial data do not support the use of non-statins in most individuals. Statins are recommended in fixed-doses to mimic clinical trials, rather than titrated (dose-adjusted) statins to achieve pre-specified low-density lipoprotein cholesterol (LDL-C) or non-LDL-C goals.[5]

In contrast, while the NLA guidelines recommend statins as the primary treatment for reducing ASCVD risk and recognize the value of fixed-dose statin therapy, they continue to recommend treatment to specific LDL-C goals and non-HDL-C goals.[6] The NLA states that treatment goals facilitate effective communication between patients and clinicians with objective, trackable outcome measures. Additionally, ASCVD risk is stratified by number of risk factors and other co-morbid conditions. The NLA risk assessment categories are low, moderate, high, and very high with a corresponding LDL-C goal of < 100mg/dL and non-HDL-C goal < 130mg/dL for all risk categories except an LDL-C goal of < 70mg/dL and non-HDL-C goal of < 100mg/dL for very high risk patients (i.e. patients with ASCVD). The threshold of high risk is ≥ 15% using the 10-year ASCVD risk assessment tool rather than ≥ 7.5% assigned by the ACC/AHA guidelines.[5, 6]

This review will focus on three patient cases commonly encountered in primary care settings where the ACC/AHA recommendations are in debate or limited. In addition, it will provide the NLA's position regarding the cases where appropriate. Case one examines risk assessment and primary prevention, case two considers statin choices in a patient with diabetes, and case three highlights treatment decisions in an elderly patient.

TABLE 1:

ACC / AHA Recommended "Statin-Benefit" Groups [5]

Statin Treatment Group	Recommended Statin Intensity	Level of Evidence *
1. Secondary prevention in patients with Clinical ASCVD	High-intensity for patients ≤ 75 years of age	A
	Moderate-intensity for patients > 75 years of age	A
2. Primary prevention in patients with primary elevations of LDL-C ≥ 190 mg/dL	High-intensity for patients ≥ 21 years of age	B
3. Primary prevention in individuals with diabetes 40 – 75 years of age and LDL-C 70-189mg/dL	Moderate-intensity	A
	High-intensity when ≥ 7.5% 10-year ASCVD risk	B
4. Primary prevention in individuals without diabetes ages 40-75 with an estimated 10-year ASCVD risk ≥ 7.5%, and LDL-C 70-189 mg/dL	Moderate or high-intensity	A

* Level of evidence "A" recommendations are derived from multiple randomized clinical trials and meta-analyses. Level of evidence "B" recommendations stem from single randomized trials or nonrandomized studies.[5]

CASE 1

A 36 year old African American female presents for her annual physical exam. She has no significant past medical history. Her father died from a myocardial infarction at age 50. She has smoked 1 pack of cigarettes per day for the past 10 years. She works as an administrative assistant and walks 20 minutes for exercise two times per week. Her blood pressure is 135/80mmHg and her BMI is 30kg/m^2. The results of her fasting lipid panel are: total cholesterol 200mg/dL, LDL-C 140mg/dL, HDL-C 50mg/dL, and non-HDL-C 150mg/dL. Her fasting blood glucose is 95mg/dL and A1C is 6.2%. What is the best approach to assess her ASCVD risk?

For this 36 year old woman, her major ASCVD risks include smoking and premature CHD in her father (see Figure 1). Her lifetime ASCVD risk totals 39% using the 10-year ASCVD risk calculator.[5, 7, 8] Her 30-year risk of ASCVD is 22%.[6]

The ACC/AHA guidelines recommend drug therapy for dyslipidemia in this age group (20 to 39 years) depending upon the patient's risk factors, preferences, and clinician's judgement.[5] In comparison, the NLA assigns a "high risk" designation to a 30-year ASCVD risk ≥ 45% in any patient with diabetes or ASCVD equivalents.[6] This patient has 2 major ASCVD risk factors and is determined by NLA standards to be at "moderate risk."[6] The NLA goals for moderate risk groups include non-HDL-C < 130mg/dL and LDL-C < 100mg/dL.[6] As mentioned previously, the ACC/AHA guidelines do not support cholesterol targets for any age group. However, a trial of lifestyle changes in low to moderate ASCVD groups is supported by both guidelines before starting drug therapy.

Recommended lifestyle changes include a reduction of saturated fat and cholesterol, smoking cessation, moderate to vigorous physical activity 45 minutes three times per week, weight loss, and referral to a registered dietician.[11]

FIGURE 1:

Major ASCVD Risk Factors [6]

- **Age** (male ≥ 45 years or female ≥ 55 years)
- **Family history of early coronary heart disease (CHD) in a first degree relative** (< 55 years male or < 65 years female)
- **Low HDL-C** (< 40mg/dL male or < 50mg/dL female)
- **High blood pressure** (≥ 140 / ≥ 90 or on blood pressure medications)
- **Current smoking**

At this patient's visit, lifestyle changes are emphasized, with a focus on smoking cessation and heart-healthy diet choices. After 3 months if cholesterol levels have not decreased despite lifestyle modifications, drug therapy is recommended for non-HDL-C ≥ 160mg/dL or LDL-C ≥ 130mg/dL.[6]

After following this patient for 5 years, she returns at age 41. She is now smoking ½ pack per day and is treated with hydrochlorothiazide for hypertension. Her current BMI is 32kg/m^2 and her blood pressure is 136/86mmHg. The results of her fasting lipid panel are: total cholesterol 260mg/dL, LDL-C 165mg/dL, HDL-C 35mg/dL, non-HDL-C 225mg/dL. Her A1C is 6.0%. Her liver function tests are in the normal range. What is the best approach to her cardiovascular risk assessment at this stage?

Since the ACC/AHA guidelines and the NLA recommend a 10-year risk calculation for patients 40 to 79 years without ASCVD, her 10-year ASCVD risk is 15.1% and 30-year risk is now 50% (increased from 39%).[8] According to the Framingham risk calculation, her 10-year risk is 14%.[6] In addition to lifestyle changes, a moderate to high intensity statin should be considered because her 10-year ASCVD risk is ≥ 7.5% and she has 3 or more major ASCVD risk factors (smoking, hypertension, family history of premature CHD, and HDL < 50 mg/dL in a female).[5-7]

Critical discussion points at this time include risks and benefits of statin treatment and patient preferences as well as a continued focus on the benefits of managing her other risk factors. For example, if she quit smoking, her ASCVD 10-year risk would decrease to 7.9%.[8] According to a Cochrane review of statins for primary prevention, drug therapy was shown to reduce all-cause mortality in patients with no history of ASCVD. They report "of 1,000 people treated with a statin for five years, 18 would avoid a major CVD event." Statins are cost effective and do not increase the risk of serious adverse effects.[12] This patient does not have characteristics commonly associated with statin adverse effects (see Figure 2). She is, however, at risk for diabetes given an A1C that suggests insulin resistance.[13]

Extended use of moderate intensity statin therapy may be associated with diabetes.[14-16] The diabetes risk with moderate intensity statins is lower than with high intensity statins and since she has such a high ASCVD risk, the benefits of preventing ASCVD likely outweigh the risks of diabetes. After a thorough discussion, she agrees to start a moderate intensity statin. When choosing a statin for her, the expected potency (dose-related lipid lowering effect) guides treatment decisions.[5] A moderate intensity statin usually lowers LDL-C by 30-49% and a high intensity statin usually lowers LDL-C by ≥ 50%. See Table 2 for a comparison of moderate and high

intensity statins. This patient should be started at the target statin dose. It is not recommended to titrate up in a stepwise fashion. Her next lipid panel should be performed in 4 to 12 weeks to assess adherence. Future lipid panels should be assessed in 3 to 12 months based on clinical judgment.

FIGURE 2:

Characteristics Associated with Statin Adverse Effects [5]

- **Multiple comorbidities**
- **Impaired renal or hepatic function**
- **History of muscle disorders**
- **History of statin intolerance**
- **Concomitant use of medications known to impact statin metabolism**
- **History of hemorrhagic stroke**
- **> 75 years**

TABLE 2:

Statin Doses and Intensity [5]

Statin^	Moderate - Intensity Daily Dose	High - Intensity Daily Dose
Atorvastatin	10 - 20 mg	40 - 80 mg
Fluvastatin	40 mg twice daily	
Lovastatin	40 mg	
Pitavastatin	2 - 4 mg	
Pravastatin	40 - 80 mg	
Rosuvastatin	5 - 10 mg	20 - 40 mg
Simvastatin	20 - 40 mg*	

^ Statins Used in RCTs: Chart modified from the 2014 NLA consensus set of recommendations for dyslipidemia and 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults

*Initiation of Simvastatin 80 mg is not recommended by the FDA because of the risk of myopathy.

CASE 2

A 58 year old Caucasian male presents quarterly for his Type 2 diabetes visit at a family medicine clinic. Other medical conditions include hypertension and dyslipidemia. He has no history of ASCVD. His medications include simvastatin 40mg at bedtime for the past five years, lisinopril 40mg daily, amlodipine 10mg daily, aspirin 81mg daily, metformin 1000mg twice daily, and insulin glargine 15 units daily. He denies tobacco or alcohol use. His blood pressure is 128/74mmHg and BMI is 33kg/m^2. The results of his fasting lipid panel are: total cholesterol 205mg/dL, LDL-C 90mg/dL, HDL-C 32mg/dL, and triglycerides 411mg/dL. A previous lipid panel is not available. The fasting blood glucose is 180mg/dL, and A1C is 10.2%. What is the best approach to address his statin therapy?

Cardiovascular disease is a major cause of morbidity and mortality in patients with diabetes.[13] The AHA/ACC guidelines recommend a moderate or high intensity statin for patients with diabetes.[5] This patient is currently receiving a moderate-intensity statin. To determine the optimal statin dosing, his current LDL-C and triglyceride levels should be considered, along with potential and current drug interactions. The ACC/AHA guidelines recommend a moderate intensity statin for primary prevention for patients with diabetes ages 40 to 75 years with an LDL-C 70 to 189mg/dL.[5] A high intensity statin is recommended when the 10-year ASCVD risk is ≥ 7.5%, although the evidence supporting this is weaker. The level of evidence is B that is derived from single randomized trials or nonrandomized studies.[5] There are no large randomized control trials in patients with diabetes that compare high intensity and low intensity statins. An additional management challenge surfaces as the 10-year ASCVD risk calculator is not intended for use in patients already taking a statin.[7]

The NLA guidelines for treatment in patients with diabetes recommend a moderate to high intensity statin irrespective of the baseline LDL-C level due to the designation of diabetes as a high or very high ASCVD risk group.[6] An LDL-C goal ≤ 100mg/dL is recommended for those with diabetes and 0 to 1 other major ASCVD risk factors as long as there is no evidence of end organ damage (defined as an albumin/creatinine ratio of ≥ 30mg/g, chronic kidney disease (CKD), or retinopathy). An LDL-C goal < 70mg/dL is recommended where there are at least two ASCVD risk factors or evidence of end organ damage. This patient has at least three risk factors: age ≥ 45 years, high blood pressure treated with medication, and low HDL-C. The American Diabetes Association (ADA) updated their standards of care to mirror the ACC/AHA guidelines.[13] For patients already on a statin in whom the baseline LDL-C is unknown, statin

trials reported that LDL-C < 100mg/dL was observed in most individuals receiving high-intensity statins.

Hypertriglyceridemia is common in patients with Type 2 diabetes, with approximately 35% having triglyceride (TG) levels ≥ 200mg/dL.[17] Elevated TG levels are typically associated with low HDL-C and small dense LDL-C particles. Type 2 diabetes can cause increased hepatic VLDL-C production due to insulin resistance.[17] The ACC/AHA and NLA guidelines classify TG as high (200-499mg/dL) and very high (≥ 500mg/dL).[5,6] TG do not become the target for primary treatment until ≥ 500mg/dL to reduce the risk of pancreatitis. However, it is not clear if there are cardiovascular benefits related to treating TG below this cutpoint. The Endocrine Society has a different classification system and classifies hypertriglyceridemia as moderate (200-999mg/dL), severe (1,000-1,999mg/dL), and very severe (≥ 2,000mg/dL).[18]

Treatment of hypertriglyceridemia in the moderate range can include statins.[5] The use of fibric acid derivatives is not recommended until TG are > 999mg/dL per the Endocrine Society.[18] The use of fibric acids, niacin, or omega-3 fatty acids are recommended for management of TG > 499mg/dL per the ACC/AHA and NLA guidelines.[5,6] Gemfibrozil should not be initiated in patients on statin therapy given the risk for myopathy and rhabdomyolysis.[5] Gemfibrozil inhibits glucuronidation which is an elimination pathway of all the statins and increases the risk of adverse effects.[19]

TABLE 3:

Simvastatin Drug Interactions [23]

Simvastatin Maximum Dose with Concomitant Medication	Concomitant Medication
10 mg	Verapamil Diltiazem Dronedarone
20 mg	Amiodarone Amlodipine Ranolazine
Contraindicated	Strong CYP3A4 Inhibitors, e.g.: Itraconazole, Ketoconazole, Posaconazole, Voriconazole Erythromycin, Clarithromycin, Telithromycin HIV protease inhibitors Boceprevir, Telaprevir Cyclosporine Grapefruit juice

Fenofibrate may be considered concomitantly with a low or moderate intensity statin if TG are ≥ 500mg/dL.[5] A recent systematic review from the Agency for Healthcare Research and Quality (AHRQ) found non-statin and statin combinations can further decrease LDL-C but no studies demonstrate additional benefit for ASCVD mortality.[20] Combination therapy is therefore not recommended for the purpose of decreasing ASCVD risk.[5] Statins should be recommended at the maximum dose tolerated before adding another drug for TG.[6] It is important to note that according to the manufacturer's product labeling, atorvastatin 40mg and 80mg daily doses can reduce TG by 29% and 37%, respectively.[21] Additionally, rosuvastatin 20mg and 40mg daily doses can lower TG by 23% to 28%.[22]

Statins vary in their drug interactions through different mechanisms in metabolism.[19] Simvastatin and lovastatin have more drug interactions since they are substrates of the cytochrome p450 3A4 pathway. Atorvastatin is a substrate for cytochrome p450 3A4 enzymes but other available routes of metabolism limit the extent of its drug interactions. Rosuvastatin, pitavastatin, fluvastatin, and pravastatin have the lowest propensity towards drug interactions.[19] The drug interactions for simvastatin are listed in Table 3.

To make a final decision regarding this patient's optimal statin dosing, his current LDL-C and TG must be considered along with his potential for drug-drug interactions. Since a baseline LDL-C is unavailable, an accurate 10-year ASCVD risk score cannot be calculated.[7] Per the NLA, the patient should have further LDL-C lowering since he is not at the goal of less than 70mg/dL and per the ACC/AHA, a higher intensity statin could be considered.[5,6] The patient's TG are moderate to high but not greater than 500mg/dL and can be further reduced with better blood glucose control and a higher intensity statin. Because the maximum dose of simvastatin in combination with amlodipine is 20mg daily, the patient is considered to be at higher risk of drug-drug interactions and adverse effects with his dose of simvastatin 40mg daily.[23] This interaction is based on pharmacokinetic studies.[24] Considering our patient's LDL-C, TG, and current drug-drug interaction, the simvastatin 40mg should be changed to atorvastatin 40mg daily or rosuvastatin 20mg daily to achieve maximal benefits with limited safety concerns.

CASE 3

A 77 year old Caucasian male newly establishes with a family physician after moving to the area. He has a history of benign prostatic hyperplasia and hypertension, managed with tamsulosin 0.4mg once daily and lisinopril 10mg once daily. He denies family history of cardiovascular disease. He reports no tobacco use for 14 years; he previously smoked 1 pack of

cigarettes per day for 45 years. His BMI is 32.6kg/m² and his blood pressure is 138/88mmHg. The results of his fasting lipid panel are: total cholesterol 221mg/dL, HDL-C 37mg/dL, LDL-C 150mg/dL, non-HDL-C 184mg/dL. The high-sensitivity C-reactive protein is 4.4mg/dL, and his comprehensive metabolic panel is within normal limits. What is the best approach to this patient's cardiovascular risk assessment and treatment?

As stated previously, the 10-year ASCVD risk calculator is validated for use in adults between the ages of 21 and 79. Based upon the data provided, this patient has an estimated 10-year ASCVD risk of 38.9%.[8] The ACC/AHA guidelines refer to the use of the 10-year risk assessment to identify statin benefit groups up to the age of 75 years.[5] This age cut point is related to the lack of clinical trial data supporting positive clinical outcomes in older age cohorts and the tendency towards a higher risk of statin-related adverse effects from drug-drug interactions and comorbidities. If the patient was younger than 75, his 10-year ASCVD risk would clearly support initiation of a statin (7.5% or higher). However, his age of 77 falls outside these parameters.

In situations of uncertainty, a patient's need for primary versus secondary cardiovascular prevention can provide clarification. For example, in the setting of secondary prevention for patients older than 75 years with clinical ASCVD, the guidelines support statin therapy but at a moderate-intensity level rather than the high-intensity statin recommended for the younger patient.[5] For primary prevention, consideration of other risk factors can facilitate decision making (see Figure 3). Notably, the guidelines do support continuation of chronic statin therapy in individuals older than 75 if well tolerated.[5] In this case, there is no evidence of a family history of premature heart disease and the LDL-C is below 160mg/dL. Data are not available for his coronary artery calcium level or ankle-brachial index, but his high sensitivity C-reactive protein is above the risk cutoff, possibly supporting initiation of pharmacotherapy for primary prevention.

FIGURE 3:

Additional ASCVD Risk Assessment Factors [5]

- **History of premature ASCVD in a first-degree relative** (< 55 years in males, <65 years in females)
- **LDL-C ≥ 160 mg/dL**
- **Coronary artery calcium score ≥ 300 Agatston units or > 75th percentile for age, sex, and ethnicity**
- **High sensitivity C-reactive protein ≥ 2 mg/L**
- **Ankle brachial index < 0.90**

To further determine whether statin therapy is appropriate, risk factors associated with adverse statin outcomes should be evaluated. Patient characteristics connected with statin adverse effects are summarized in Figure 1 *(page 39)*. To facilitate this evaluation, baseline measurement of liver transaminase levels (specifically alanine transaminase or ALT) is recommended in all patients prior to statin initiation.[5] Baseline measurement of creatine kinase is only warranted in those at risk for statin related myopathy, such as a history of statin intolerance or concomitant use of drugs that interact with statins.[5] This patient's initial laboratory testing reveals normal renal and liver function. He does not report a history of muscle disorders or other conditions or medications that would indicate potential issues with statin safety.

Based upon this patient's 10-year ASCVD risk, elevated high sensitivity C-reactive protein, and what appears to be a low propensity for adverse statin effects, it is decided to initiate a moderate intensity statin. He starts atorvastatin 10mg once daily. It is also noted that counseling for other cardiovascular risks should occur at this time, including assessment of eating and physical activity habits to encourage weight loss with his obese body mass index.

The patient presents to clinic for follow-up after one month. He reports adherence to his daily dose of medication but complains of muscle discomfort that he describes as "weakness" in both legs since initiating the statin. He denies any other symptoms at this time. What is the best approach to his symptoms?

The ACC/AHA guidelines recommend against routine laboratory monitoring after statin initiation.[5] However, assessment of symptoms of myopathy such as muscle pain, tenderness, cramping, weakness and fatigue should be performed at follow-up visits. Measurement of creatine kinase in symptomatic patients is necessary to investigate potential causes. Measurement of liver transaminases should occur if a patient complains of symptoms associated with hepatotoxicity such as abdominal pain, loss of appetite, dark-colored urine or yellow skin/sclera. Routine measurement is no longer supported. An additional monitoring parameter especially pertinent in the older population is evidence of statin-associated memory impairment or confusion.[5]

The ACC/AHA guidelines recommend a structured approach for management of muscle-related statin symptoms.[5] First, the statin should be discontinued during the evaluation process. Other causes should be investigated and ruled out, including vitamin D deficiency, rheumatologic disorders, or hypothyroidism. Based upon this patient's complaints, a creatine kinase level should be ordered.

The statin may be reinitiated at the same or lower dose if the symptoms resolve during this time in order to re-challenge the symptoms. If they recur, the statin should be discontinued and a lower dose of a different statin may be initiated once the symptoms resolve again. Increased doses of this statin can be attempted if the lower doses are tolerated.[5] All planning should involve discussion of patient preferences and re-evaluation of individualized risks and benefits that can change over time, especially in the elderly.

The limited data guiding the use of statin therapy in older individuals identifies several gaps requiring further research. Enrollment of adequate cohorts of men and women over age 75 in clinical trials is necessary to document clinical outcomes for both primary and secondary prevention of cardiovascular disease. Evaluation of clinical outcomes from alternative regimens utilized in statin-intolerant individuals, such as lower doses or non-statin medications, will further facilitate safe and effective care in patients of all ages.

CONCLUSION

ASCVD risk should be evaluated in all adult patients as ASCVD is the leading cause of death in the United States. Statins are important for the primary and secondary prevention of ASCVD. The Mayo Clinic has a useful online tool for demonstrating the primary prevention benefits and risks of statins.[25] Further research is needed to evaluate the benefits of statins in younger and older patients and better determinates on selection of statin intensity in a patient with diabetes.

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REVIEW ARTICLE

Unipolar & Bipolar Disorder: A Primary Care Perspective

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Mood disorders are a group of mental health conditions that afflict an estimated 21 million American adults each year. Due to the high incidence of mood disorders, including depression and bipolar disorder, in the general population, a family physician must be prepared to recognize and appropriately evaluate, diagnose and treat, a patient with a persistent alteration in their mood. This article will provide a general overview of two major types of mood disorders: unipolar and bipolar disorders, and will provide primary care physicians with additional tools for approaching such conditions in the adult population.

INTRODUCTION

In a given year, approximately 20.9 million Americans or nearly a tenth of Americans, aged 18 and older, suffer from a mood disorder.[1, 2] The vast majority of all patients suffering from a mood disorder present to the primary care physicians' office first, and sometimes, they never follow up with a psychiatrist. Despite a substantial segment of the American population being impacted, this group of mental disorders remains among the most difficult to diagnose and treat in the primary care setting. One of the most common reasons is thought to include the primary care physician's lack of fluency and/or aid in distinguishing the fine line between normal variation and mental disease. However, an even more significant factor may also be consternation, borne of compassion, about rendering a psychiatric disorder diagnosis, which still carries a significant social stigma and may further complicate daily life for the patient.

In this article, we will attempt to provide guidance to enhance the primary care physician's ability to and confidence in diagnosing, treating, and if necessary, referring a patient to a psychiatrist, with a particular focus on unipolar depression and bipolar disorders. While this article will not eradicate the social stigma associated with these illnesses, we hope that earlier detection may help patients' to better cope with their condition before it may become debilitating and in a subset cause the attempts and completions of life ending measures.

IMPACT

UNIPOLAR DEPRESSION

Unipolar depression is an umbrella term that includes several disorders such as dysthymic disorder and major depressive disorder, the latter being the leading cause of disability among Americans ages 15-44.[3] In a given year, nearly 14.8 million American adults, or about 6.7 percent of the American population age 18 and older suffer from major depressive disorder.[1, 2] Major depressive disorder can arise at any age but the average age of onset is 32.[4] Women are two times more likely to develop major depression disorder and have a lifetime risk of 20% versus 10 % in males.[5, 6] On the other hand, dysthymic disorder has an incidence of 1.5% for the American adults.[1] The most recent census data suggest the current adult population 18yo+ is 239,516,413 and this suggests 3,592,746 adult Americans currently suffer from this condition.[2] The median age of onset for dysthymic disorder is 31.[1]

BIPOLAR DISORDER

Similarly to unipolar depression, bipolar disorder also afflicts a significant number of people both in America and worldwide.

- The World Health Organization ranks bipolar disorder as the sixth leading cause of disability among people ages 15-44.[3]
- In a given year, 8,161,765 American adults, or about 2.6% of the population age 18 and older, are affected by bipolar disorder.[1, 2]
- The median age of onset for bipolar disorders is worryingly young at just 25 years.[4]

ETIOLOGY

Due to the multifactorial etiology of unipolar and bipolar disorders, treatment requires a deep understanding of the mood disorders, along with an intricate balance of skill that providers must possess to successfully treat such ailments.[7] Although there is a particularly strong link that exists between family history and diagnosis of unipolar and bipolar disorders; due to their historical under recognition and under diagnosis, it is not so simple for a physician to collect a history with

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positive family history with a diagnosis of a mood disorder. Therefore, the physician must also look to a family history of an undiagnosed unipolar or bipolar disorders.

- Patients who have first-degree relatives with major depression should be observed more closely for symptoms of unipolar and bipolar disorders.[5]
- Patients with one parent who is bipolar have a risk of 27% to 29% of developing the disorder; while patients with two affected parents have a 50% to 74% chance.[5]
- Studies using monozygotic twins as subjects show that the genetic contribution to developing major depression is 37%, while that of developing bipolar disorder is 80%.[7]

CLINICAL PRESENTATION

As a primary care physician, once you suspect your patient is suffering from a mood disorder, it will become critical to try to eliminate other possible mood disorders as possibilities, and then to distinguish unipolar depression from bipolar disorder. Unlike a variety of physical illnesses that can be observed and diagnosed at an isolated point in time, an accurate diagnosis of mood disorder requires a thorough history of symptoms prior to as well as presenting at the visit. This can be a daunting task for physicians; most notably due to time limitations and heavy patient reliance on historical clues. A sound rapport with the patient is thus an essential component to successful diagnosis and treatment of patients with mood disorders. Refer to Tables 1 and 2 for presenting symptoms of depression and mania.

UNIPOLAR DEPRESSION

Unipolar depression most often appears in the form of major depressive disorder and/or dysthymic disorder. Common presentations for major depression include depressed mood, lack of interest in things once pleasurable (also termed anhedonia), changes in sleep, decreased concentration and energy, significant changes in weight, feelings of hopelessness and guilt, psychomotor agitation or retardation, and recurrent thoughts of death. According to the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), the criterion for diagnosis is five or more of the aforementioned symptoms being present for at least two weeks. Patients do not have to admit to a depressed mood to be diagnosed with major depression but if they don't admit to a depressed mood, they must admit to anhedonia.[8]

Note, when screening for unipolar disorder, one must also rule out bipolar disorder.

BIPOLAR DEPRESSION

Bipolar disorder is classified as either Type I or Type II. Bipolar disorder has recurrent episodes of depressed mood with each episode lasting at least 2 weeks. In bipolar Type I disorder the patient has both mania (severely elevated mood causing impairment of judgment such as law disobedience) and depression, while only one manic episode is necessary for this diagnosis. In bipolar Type II disorder patients have episodes of both hypomania (mild elevation in mood without causing impairment of judgment) and depression.[8]

In contrast to bipolar Type II disorder, patients need not have any history of depression in bipolar type I diagnosis.

For the diagnosis of a manic episode, either hospitalization or 3 of the symptoms in Table 2 must be presenting in the patient and can be easily recalled with the acronym DIG FAST.

TABLE 1:

Presenting Symptoms of Depression

Symptoms of Depression "People From SAD CREW"
Psychomotor agitation or retardation
Feelings of hopelessness or guilt
Sleep changes
Anhedonia
Depressed mood
Concentration(decreased)
Recurrent thoughts of death
Energy (decreased)
Weight changes

TABLE 2:

Presenting Symptoms of Mania

Symptoms of Mania "DIG FAST"
Distractibility
Irresponsibility
Grandiosity
Flight of ideas/Increased goal oriented activity
Agitation (Psychomotor)
Sleep (decreased need)
Talkativeness/pressured speech

Carlat, D. The psychiatric review of symptoms: a screening tool for family physicians. American Family Physician 58(7): 1617-1624, 1998.

SCREENING

The U.S. Preventative Services Task Force (USPSTF) recommends screening all adult and pediatric (age 12-18) patients for depression when the physician has services in place to ensure correct diagnosis, favorable treatment, and follow up.[9, 10]

Physicians have several options at their disposal to utilize for screening purposes, from simple self-reported questionnaires to more complex instruments.

We have found self reporting screening tests to be quite convenient and accurate for the proper diagnosis of unipolar disorder. The simplest of these screening tests consists of one question that asks "are you depressed?"

The PHQ-2, a two question screening test, addresses the patients' mood and anhedonia. The questions are:

- During the past month, have you been bothered by feeling down, depressed, or hopeless?
- During the past month, have you been bothered by little interest, or pleasure doing things?

Longer self-reporting screening tools used include:

- Zung Self-Rating Depression scale
- The PHQ-9
- Beck Depression Inventory (BDI-II)
- The Center for Epidemiologic Studies-Depression Scale (CES-D).

With the exception of the PHQ-9, the above tests must be followed up with a full clinical interview focusing on psychiatric history. The PHQ-9 asks each specific symptom of major depression and therefore establishes the diagnosis of major depression without any requirement for further confirmation. This screening test can also be used to track patient symptoms and responsiveness to treatment. The above-mentioned questionnaires are available at www.depression-primarycare.org/clinicians.

The previously mentioned screening tests are all based on patient self-reporting. Another widely used screening test is the Hamilton Depression Scale (HDRS). Unlike the other screening tests, HDRS requires a trained professional to administer it. The results of the HDRS are positively correlated to the BDI-II with a Pearson r of 0.71, meaning there is more than a 70% chance of the same diagnosis using either screening tool.[11]

Currently, there are no fixed screening guidelines for bipolar disorder, except when considering use of Antidepressants or when the patient presents with conclusive symptoms of bipolar or unipolar.

Mood Disorder Questionnaire (MDQ), a one-page questionnaire that covers symptoms, timing and duration. Some other useful screening tools include the Bipolar Spectrum Diagnostic Scale, the My Mood Monitor Checklist (also called M-3). The above stated screening methods are available at www.dballiance.org/pdfs/MDQ.pdf. It is important to recognize the resources listed above possess a high negative predictive value and thus are good at ruling out mood disorders but by no means do they suffice to confirm a diagnosis.[12] When suspecting bipolar disorder, all other etiologies first must be ruled out before diagnosis of bipolar disorder can be made.

A majority of bipolar patients self-report their self-assessment of depression to their primary care physicians. Rather than reporting the mania present, it is often misdiagnosed as having unipolar depression. Up to 30% of patients exhibiting depressive symptoms actually may have a bipolar disorder.[13] It bears repeating that a patient does not need to have any history of depression to be diagnosed with bipolar Type I disorder and the requirement that the individual simultaneously meet full criteria for both mania and major depressive has been removed from DSM-V.[14] Signs that should alert the primary care provider to bipolar disorder in a patient with depressive symptoms, include a family history of bipolar disorder, precipitation of a hypomanic or manic episode in response to an anti-depressant treatment, symptoms arising before age 25, failure to respond to three or more trials of an antidepressant medication, abrupt onset and offset of episodes, possible seasonal pattern or the presence of atypical depressive symptoms such as hypersomnia.[15]

EXCLUDING OTHER CAUSES

It is important to note, before making a mood disorder diagnosis, one must rule out physical causes such as thyroid disease and anemia. This can be easily performed by ordering a complete blood count and a thyroid stimulating hormone level. In addition to the above labs, in the elderly patient, workup should also include a vitamin B12 level, a serum folate, and a rapid plasma reagin.[16] B12 and folate deficiencies can present with depressive symptoms mimicking a mood disorder. One must look closely at the patient's medication list to rule out medication-induced conditions. Some common medicines that can cause depression-like features are antihypertensives (such as beta-blockers), methyldopa (Aldomet) and clonidine (Catapres).[17] Digitalis may also cause such symptoms. Parkinson's disease drugs

and interferon have also been linked to emerging depressive symptoms.[17] 50% of patients treated with interferon (Pegasys), experience a major depressive episode and it is now recommended prior to starting interferon therapy to prophylactically start the patient on antidepressants, especially if the patient also has a history of depression.[18] Other medications that have been associated with changes in mood are corticosteroids and oral contraceptives.[17] Symptoms of depression often co-exist with other health conditions and comorbidities. 10% to 15% of all depression is attributable to chronic medical illnesses such as renal disease, Parkinson's disease, cancer, diabetes, heart disease and stroke.[18] Thus, with an ever-increasing geriatric population, primary care physicians are destined to see increasing numbers in their future practice.

Refer to Table 3 for other etiologies of mood disorders.

TREATMENT

Treating mood disorders promptly enhances the patient's health prospects through reduction of the risk of relapse and an increased response rate to medications. Therefore, when properly screened and diagnosed early, treatment can help control their serious distress, and/or social/occupational impairments. Please refer to Table 4 (*page 48)* and Table 5 (*page 51*) for a summary of commonly used medications to treat depression and mania, as well as known side effects of these medications.

TABLE 3:

Other etiologies of mood disorders (Mnemonic "Nine Hand")

Categories	Examples
Neurologic	CVA, Parkinson's, Alzheimer's/other dementia, Seizures, Multiple sclerosis, Huntington's
Infectious	HIV, Syphilis
Neoplastic	Pancreas, Brain tumor
Endocrine	Thyroid, Hypothalamic-pituitary-adrenal disorders
Hematologic	Acute intermittent porphyria, Anemia
Autoimmune	Neuropsychiatric systemic lupus erythematosus, Rheumatoid Arthritis
Nutritional	B12, Folate deficiencies
Drugs	Illicit drugs, Prescription medications such as steroids, beta blockers, interferon

UNIPOLAR DEPRESSION

According to the American Psychiatric Association's Practice Guideline for the treatment of patients with depression, three phases exist in the treatment of major depression.[19] The first phase is called the acute phase, during which the goal is to put the patient into remission. This is accomplished by carefully selecting the appropriate treatment: psychopharmacology, psychotherapy, or electro-convulsive treatment (ECT).

When considering treatment via pharmacology, it is important to keep in mind the cost of drug, severity of symptoms, side effect profile, and prior response to pharmacological treatment. Patient autonomy is an important contributor in guiding the physician to prescribe appropriate treatment, especially for mild to moderate depression where symptoms and side effects must be weighed.

Some patient presentations that may lead the physician to consider starting with psychopharmacology are: "prior response to medication, moderate to severe symptomatology, preference of patient, significant sleep or appetite disturbance, or agitation."[19] Clinical features that should encourage starting with psychotherapy are: "prior positive response to therapy, co-occurring axis II disorders, mild-moderate symptoms, and significant psychosocial stressors" in which the patient would benefit from therapy.[19]

The main classes of antidepressants that are recommended as first line therapy are selective serotonin reuptake inhibitors (SSRIs), atypical antidepressants such as bupropion (Wellbutrin) and mirtazapine (Remeron), selective norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants. Monoamine oxidase inhibitors (MAOIs) have also been used in the past but are no longer first line therapy. With each class of medication, there are side effects that should be carefully explained to the patient. With TCAs, the side effects to consider are cardiac arrhythmias (QTc prolongation), anticholinergic effects, and sedation. With the SSRIs, the main class side effects are sexual dysfunction, weight gain, and nausea/vomiting. With the SNRIs, the most common side effects are hypertension, and diaphoresis. Mirtazapine's side effects include severe weight gain due to appetite stimulation, as well as sedation. Bupropion side effects include insomnia and decreased seizure threshold. For patients that are smokers, consider the use of bupropion since this medication also has proven efficacy for smoking cessation.

Psychotherapy, such as cognitive behavioral therapy, can be used to treat mild or moderate depression in conjunction with medication.[20] Also, psychotherapy should be considered as first line treatment in women who are breastfeeding, pregnant, or wish to become pregnant. However women with severe depression (suicide attempts, functional incapacitation,

TABLE 4:

Major Depression treatment choices and its side effects

Class of Medication	Side Effects
Selective serotonin reuptake inhibitors: Fluoxetine (Prozac) Sertraline (Zoloft) Paroxetine (Paxil) Fluvoxamine (Luvox) Citalopram (Celexa) Escitalopram (Lexapro)	Dizziness, Headaches, Gastrointestinal, Sexual dysfunction
Selective neuroepinepherine reuptake inhibitors: Venlafaxine (Effexor)	Headache, Nausea, Vomiting, Diarrhea, Sweating, Increased blood pressure
Duloxetine (Cymbalta)	Dry mouth, Nausea, Constipation, Decreased appetite, Insomnia, Sweating and Dizziness
Atypical antidepressants: Bupropion (Wellbutrin)	Headache, Dizziness, Decrease seizure threshold, Weight loss
Mirtazipine (Remeron)	Sedation, Weight gain, Increased appetite, Agranulocytosis, Somnolence
Trazodone (Desyrel)	Sedation
Tricyclic antidepressants: Amitriptyline (Elavil) Imipramine (Tofranil) Nortriptyline (Pamelor)	QT prolongation, Sedation, and Anticholinergic effects

or weight loss) may need to be started on antidepressant medication if the benefits outweigh the risks.[21] It is important to recognize that during the acute phase, patients are going to be symptomatic, which in turn would lead them to be poorly motivated and pessimistic during treatment; this could subsequently affect adherence to medication.

Once any modality of treatment has been started, usually 4 to 8 weeks are given to evaluate whether a particular treatment is working. If there is absolutely no change in symptoms after 4 weeks, the treatment must be modified. In patients being treated solely with anti-depressant medication, slowly increasing the dosage of the current medication is the first step, providing the patient can tolerate the side effects, keeping in mind that suicidal/homicidal risk must be assessed at each visit. If the patient cannot tolerate the increase in dosage of medication or prefers not to increase the dosage, the alternative is to switch the patient to another non-MAOI anti-depressant medication in the same class or a different class. For those patients that have more complex disease with symptoms not controlled on one agent, it might take two different medications to treat the patient's symptoms adequately. In this case, one would add a second non-MAOI anti-depressant of a different class then the initial drug. For example, adding bupropion to an SSRI. Other options of medications to add would be lithium or a second-generation anti-psychotic.

If the patient is still not responding to treatment, they most likely have treatment-resistant depression in which case, ECT is the most effective form of treatment. If a patient's symptoms are partially improving, it is reasonable to wait another 4 to 8 weeks before making any adjustments to the medication. In patients being treated solely with psychotherapy that are having no change in symptoms, the next step is to increase the frequency of the therapy session. ECT is performed two to three times per week. Usually, an acute course of ECT lasts from two to four weeks. ECT has the highest rate of response and remission out of all the other treatment modalities with 70% to 90% of patients getting better.[19]

TABLE 4.1:

Treatment of Unipolar depression - 3 Phases

	Goal	Options	Considerations	Time
Phase 1: Acute	**Remission**	**Pharmacology** **Psychotherapy** **Electro-convulsive treatment**	Cost Severity of symptoms (i.e. sleep or appetite disturbance) Side effects Prior response to treatment type Patient autonomy	4 - 8 weeks modify treatment if no change in 4 weeks
Phase 2: Continuation of Treatment			Monitor for signs of relapse	4 - 9 months
Phase 3: Maintenance			Determine if treatment can be discontinued Factors: • Risk of reoccurrence • Co-existing conditions • Persistence of symptoms	Patient specific

The second phase of treatment is the continuation phase. This phase lasts for 4 to 9 months and the patient is kept at the same dosage of medication used to achieve remission during the acute phase. It is important during this phase to monitor for signs of relapse.

The third and last phase of treatment is the maintenance phase. It is important to make a determination of whether following the continuation phase the patient will likely need to continue the medication. Patients that are euthymic generally focus on the burden and side effects of treatment, while not noticing the benefits. Recurrence is common and occurs in approximately 20% of patients within the first six months following remission. Over a patient's lifetime, they have a 50% to 85% chance of having at least one recurrence.[19] Risk factors to recurrence include earlier age of onset of symptoms, prior history of major depressive disorder, and ongoing sleep disturbances. Patients who have had three or more major depressive episodes should receive maintenance treatment.

There have been no studies on exactly how and when to discontinue treatment in patients that no longer want treatment. Factors that need to be considered are risk of recurrence, other co-existing conditions, persistence of symptoms after remission has been reached. Patients need to be advised not to abruptly discontinue anti-depressants and that the medication needs to be tapered over several weeks. Symptoms that the patient could experience if they suddenly discontinue medication are flu-like symptoms and headache. It is also important to educate the patient that recurrence of symptoms is highest within the first two months of discontinuing treatment. Please refer to Table 4.1 for a summarized view of how to treat unipolar depression.

BIPOLAR DISORDER

The standard of care treatment for patients with bipolar disorder is a mood stabilizer.[22] It is contraindicated to have a patient with bipolar disorder on monotherapy with an antidepressant. Current guidelines recommend that a patient should be on a mood stabilizer regardless of which phase the patient is presenting in.[23] Treatment for bipolar disorder consists of two stages: acute and maintenance. In the acute phase, it is important to choose an appropriate medication for the medication naïve patient. First line medications that are being used to treat mania are lithium (Lithobid), valproate (Depakote), and second-generation anti-psychotics. For a patient that is presenting with acute severe mania or a mixed episode (patients that present with both elevated and depressed mood symptoms at the same time), it is recommended to start lithium or valproate in combination with a second-generation antipsychotic.[22] For patients with less severe symptoms, monotherapy would be adequate with lithium,

valproate, or a second-generation antipsychotic. Valproate is the drug of choice in patients presenting with mixed episodes. If the patient is currently on an antidepressant medication, that medication should be tapered and discontinued. Patient symptoms must be monitored closely within the first 10 to 14 days of treatment to assess for suicidal/homicidal tendencies since the risk may be increased in some patients (see section 9: suicide risk). If symptoms are inadequately controlled with optimized dosages of medication, then addition of another first line agent is necessary.[22]

For a patient that is bipolar and presenting in acute depression that has not been on any treatment modality before, first line treatment is lithium or lamotrigine (Lamictal). When using lamotrigine, the expected response time is approximately 3 weeks.[24] It is not recommended to have the patient on monotherapy with an antidepressant. If a patient fails to respond to optimized treatment, the addition of bupropion, lamotrigine, or paroxetine should be considered. Studies have shown that the use of antidepressants in patients that have a diagnosis of bipolar Type II is higher than in bipolar Type I due to "lower rates of antidepressant-induced switching into hypomania or mania."[22] For a patient that is rapid cycling (4 or more cycles/year of either manic, hypomanic, major depression, or mixed depression) it is important to identify and treat any medical condition that could contribute to the rapid cycling. Also, it is important to taper patient off antidepressants that possibly could be contributing to the rapid cycling. Initial treatment consists of either starting lithium or valproate. Lamotrigine could also be used as an alternative. In most cases of rapid cycling, multiple medications are required to control the symptoms. Either a combination of two mood stabilizers (lamotrigine, valproate, or lithium) or one mood stabilizer plus a second generation antipsychotic are used.[22]

The goal of the maintenance phase of treatment is to reduce suicide risk and prevent relapse of symptoms. Maintenance medication is recommended after a depressive episode or a manic episode in a patient that has a diagnosis of bipolar disorder. The best evidence supports use of lithium or valproate for maintenance treatment, but lamotrigine, or carbamazepine can be used. The medication that was used during the most recent depressed or manic episode that led to remission should be continued. Antipsychotic medication can be discontinued during this phase unless needed for continued psychosis management. Maintenance therapy has been done with antipsychotics, but less evidence exists for the efficacy as does for the mood stabilizers. If during the maintenance phase, the patient continues to experience sub-threshold symptoms, another maintenance medication, second generation antipsychotic, or antidepressant should be added.[22]

In prescribing medications to treat bipolar disorder, it is important to know how to monitor the medication and the side effects of each one. The most recognized mood stabilizer used is lithium. Lithium is approved for use in both the acute phase and the maintenance phase of the disease.[14] Lithium's side effects include polyuria, polydipsia, weight gain, tremor, sedation, and gastrointestinal distress. Lithium can also cause diabetes insipidus, thyroid abnormalities and birth defects. A majority of patients will experience some side effects from lithium but most are minor and can be eliminated by changing the dose schedule or lowering the dose. It is important to monitor renal and thyroid functions, as well as lithium and sodium levels, while the patient is on lithium. Certain labs should be checked when there is a change in the patient's presentation. For a stable patient, lithium levels should be checked every six months. The therapeutic serum level is between 0.8 to 1.2 meq/L and it is suggested that serum levels be assessed five to seven days after each increase in dosage.[25] Renal function should be checked every 8 to 12 weeks for the first six months when the patient is first placed on the medication. After that time period, renal function can be checked every 6 to 12 months if the patient is stable. Thyroid function should be checked at least twice within a six-month period upon initiation of treatment with lithium. After that time period, the thyroid can be checked every 6 to 12 months if the patient is stable.[22] It is also important to note that Lithium has an extremely narrow therapeutic index, so patients on Lithium must closely be observed.

Valproic acid is another mood stabilizer used to treat bipolar disorder. It has shown a greater efficacy in treating mania in the acute phase, in contrast to maintenance therapy. Valproate's side effects include gastrointestinal distress, weight gain, elevated liver enzymes, and sedation. Mild leukopenia and thrombocytopenia can also occur but are reversed with discontinuation of the medication. It is important to monitor blood count and liver function tests in these patients. Liver function tests and complete blood count should be performed every six months at a minimum for stable patient. Valproate levels should be checked when suspicions of non-compliance are present or when a patient is placed on any other medication that could change the metabolism of valproate (carbamazepine, carbapenem antibiotics and lamotrigine can decrees valproic acid levels while amitriptyline, diazepam, ethosuximide, phenytoin, and phenobarbital may increase levels). It is also important to keep in mind that if one is considering having the patient on both lamotrigine and valproate, the dose of lamotrigine must be started at half of the normal starting dose because valproate inhibits metabolism of lamotrigine.[22]

TABLE 5:

Biopolar Disorder treatment choices and side effects

Class of Medication	Side Effects
Mood Stabilizers: Lithium (Lithobid)	Polyuria, Polydipsia, Weight gain, Tremor, Sedation, Gastrointestinal distress, Diabetes Insipidus, Thyroid abnormalities, Congenital anomalies (Ebstein's anomaly)
Valproic Acid (Depakote)	Gastrointestinal distress, Weight gain, Elevated liver enzymes, Sedation, Mild leukopenia and Thrombocytopenia
Carbamazepine (Tegretol)	Gastrointestinal distress, Dizziness, Drowsiness, Elevated liver enzymes, Fatigue
Lamotrigine (Lamictal)	Headache, Nausea, Infection, Xerostomia, and Rash
2nd Generation Antipsychotics: Aripiprazole (Abilify), Ziprasidone (Geodon), Risperidone (Risperdal), Quetiapine (Seroquel), Olanzapine (Zyprexa)	Weight gain, Hyperlipidemia, Hyperglycemia, Cardiac arrhythmia (QTc prolongation), Sedation, and Hypotension

Another mood stabilizer found to be efficacious in treating bipolar depression in the acute phase is lamotrigine. It has also been found to be effective in the long-term management of bipolar disorder especially in managing recurrent depression.[26] Most common side effects of lamotrigine are headache, nausea, infection, and xerostomia. Patients need to also be educated about the possibility of developing a rash. Although a rash could occur at any time once starting treatment, usually it occurs within the first few months. Rashes that should be considered extremely alarming are those accompanied by fever, sore throat, those involving the face or mucosa, and those that are wide spread over the body. In this case, lamotrigine needs to be discontinued. To minimize the risk of a rash, lamotrigine is started at a low dose and titrated up very slowly. Lamotrigine can also lead to Steven-Johnson syndrome, which is a life threatening condition.[22]

Some atypical antipsychotics have also been shown to be efficacious for the treatment of bipolar disorder. These include quetiapine (Seroquel), risperidone (Risperdal), and olanzapine (Zyprexa). Common class side effects to the second-generation antipsychotics include weight gain, hyperlipidemia, hyperglycemia, cardiac arrhythmia (such as QTc prolongation), sedation, and hypotension. It is important to monitor blood glucose and lipids in these patients, as the use of atypical antipsychotics can lead to an increased risk of diabetes and hypertriglyceredemia.[22] In the case of acute bipolar depression, studies have shown it to be safe to use olanzapine with fluoxetine (Prozac).[27] Please refer to Table 5.1 (*page 52)* for a summarized view of how to treat bipolar disorder.

REFERRING TO A SPECIALIST

The primary care physician must be knowledgeable in making a diagnosis of unipolar and bipolar disorders, and must be familiar with the mainstay initial treatment options, but must also recognize when to refer the patient to a psychiatrist for further evaluation and treatment. Some situations in which a primary care provider should consider referring the patient to a specialist include:

- Severe depression accompanied by life threatening situations involving the patients' lives or the lives of their dependents
- Symptoms not alleviated by initial trials of antidepressants
- The presence of psychotic symptoms
- Depression that is "part of the course" of another major psychiatric illness such as bipolar disorder or schizoaffective disorder.[16]

TABLE 5.1:

Treatment of Bipolar depression - 2 Phases

	Goal	Options	Considerations	Time
Phase 1: Acute	**Remission**	**Pharmacology - mood stabilizer**	Cost Severity of symptoms Side effects Prior response to treatment type Patient autonomy Co-morbidities (i.e. diabetes)	Monitor closely first 10 - 14 days Response within 3 weeks
Phase 2: Maintenance	**Reduce suicide risk; Prevent relapse**	**Pharmacology**	Side effects	Lifetime Check renal and liver functions regularly

SUICIDE RISK

At the time of evaluation of a mood disorder, one must also always assess for the risk of suicide including ideation, plan and intent. It is estimated that as many as 25% to 50% of patients with bipolar disorder attempt to commit suicide.[28] Many patients suffering from unipolar depression actually succeed in committing suicide. According to a study by Angst et al., the incidence of suicide is 27 times greater in patients with unipolar depression, as compared to the general population.[29] Evaluating your patient for suicidality is crucial and, in certain cases, it may become necessary to involuntarily commit a patient that is in your office for psychiatric treatment. It is also important to remember that antidepressants have been shown to increase the risk of suicidal thinking and behavior in some children, adolescents, and young adults in short-term studies of major depressive disorder.[30] This has generally occurred during initial treatment usually within the first one to two months.

CONCLUSION

Mood disorders, such as depression and bipolar disorder, are under diagnosed and undertreated; therefore, screening, in a primary care setting is critical and should be routine. We suggest that practitioners screen patients for depression periodically, particularly when anxiety, chronic conditions, and somatic complaints are present. As a primary care physician, it is important to become familiar with and be able to distinguish unipolar from bipolar disorder, as patients experiencing symptoms of depression, mania and hypomania will primarily present to their primary care's office first and it will be the duty of that physician to properly diagnose, treat and refer the patient.

Although the new standard of diagnosis mental disorders is made by the DSM V, no significant changes have been made from the DSM IV in terms of symptoms or duration of symptoms.[31]

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CLINICAL IMAGES

Phytophotodermatitis

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A five year old boy accompanied by his concerned mother presented to the local emergency department fast track with an erythematous skin rash in a drip-mark configuration on his shoulders, upper arms, trunk, and back (Fig. 1 & 2). The mother noticed the rash the same day of ED arrival. The child had just spent the weekend with his father and the mother was aware that the child had been playing outdoors. There were no other known exposures. The mother denied fever, pruritus, lesions on palms or soles, oral lesions, recent bug bites, or others in the household with a similar rash.

The father was then called and provided further history. He revealed that two days prior to appearance of the rash he attempted to rid his son of head lice by pouring a homemade solution of lemon juice and hydrogen peroxide on his head. The patient proceeded to play outside in the sun that day without a t-shirt on.

FIGURE 1:

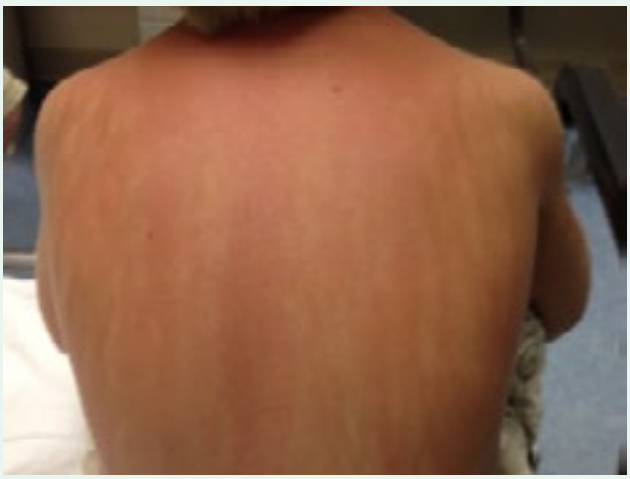
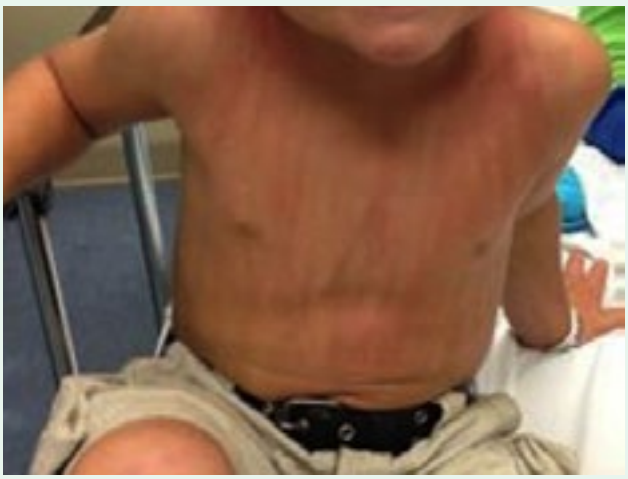


FIGURE 2:



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QUESTIONS

1. What is the diagnosis?

    a. Folliculitis
    b. Dermatitis Herpetiformis
    c. Phytophotodermaditis
    d. Atopic Dermatitis
    e. Rhus Dermatitis

2. What is the mechanism of the rash?

    a. Inflamed and infected hair follicles
    b. Autoimmune
    c. Contact with photo-reactive compounds
    d. Dietary exposure
    e. Poison ivy exposure

3. What is the recommended treatment for this patient?

    a. Conservative, symptomatic care, wet dressings
    b. Oral Prednisone
    c. Topical Prednisone
    d. Bleaching agents
    e. Oral antibiotics

See page 56 for answers and discussion.

ANSWERS

1. What is the diagnosis?

Answer C: Phytophotodermatitis

Explanation: The patient had skin exposure to a citrus solution when his parent was attempting to rid him of lice. He subsequently had UV light exposure playing outdoors without a shirt on. The other answers are incorrect because: Folliculitis is a papular rash localized to hair follicles. Dermatitis herpetiformis is a pruritic rash with bumps or blisters most often localized to the elbows, knees, back and buttocks. Atopic dermatitis is a pruritic, sometimes painful and weeping rash that often begins in the creases of elbows or knees. It can progress to scaling patches and pigmentation changes. Rhus dermatitis should be distinguished from a blistering presentation of phytophotodermatitis. Rhus dermatitis is not limited to sun-exposed areas of the body and may continue to worsen over the course of one or two weeks, while phytophotodermatitis will peak in intensity in 48-72 hours and leave behind a post-inflammatory hyperpigmentation.

2. What is the mechanism of the rash?

Answer C: Photoreactive componds

Explanation: Phytophotodermatitis is caused by photoreactive compounds in certain plants that cause inflammation of the skin when exposed to UV light.

3. What is the recommended treatment for this patient?

Answer D: Conservative, symptomatic care, wet dressings

Explanation: Rem Management depends on the area of skin involvement as well as the intensity. In mild cases, the treatment is conservative, symptomatic care with moist dressings. If the dermatitis is severe, involving more than 30% of total body surface area, the patient may need burn center evaluation. Topical or oral corticosteroids may help with patient discomfort. Sunscreens containing physical blockers of UV-A radiation such as zinc oxide and titanium dioxide are recommended to prevent further epithelial damage and inflammation. Bleaching agents such as hydroquinone are rarely indicated as the hyperpigmentation will fade over the several-month healing process.[10]

DISCUSSION

Phytophotodermatitis is a non-immunologic inflammatory skin reaction which develops following cutaneous contact with photoactive compounds in certain plants called furocoumarins in conjunction with sunlight exposure.[1] The furocoumarins, most commonly psoralens and angelicins, found in various plants and plant extracts form phototoxic combinations when exposed to ultraviolet-A radiation.[2] The phototoxic cutaneous reaction occurs most frequently after contact with citrus fruit juices, celery, and rue.[1] Because of the association with citrus fruits, the condition is also referred to as "Lime Disease" or "Margarita photodermatitis."[3]

Phytophotodermatitis dates as far back as 2000 BC when the practice of rubbing juices from Ammi majus on the skin was encouraged for patients suffering from vitiligo, an autoimmune condition of skin depigmentation.[1] In 1400 BC, Psoralea corylifolia was boiled and used on these patients to induce the skin dermatitis and subsequent hyperpigmentation, from which the term "psoralen" was named.[1] However, it was not until 1942 that the combination of plants and sunlight as a cause of the phototoxic reaction was recognized and termed "phytophotodermatitis" by Robert Klaber, M.D.[1] The plants that are largely responsible for the sun-induced skin rash include: the Umbelliferae family, which includes celery, parsley, and parsnips; the Rutacea family, which includes lemons and limes; and the Moraceae family which includes figs. In current times, the skin condition is common in children during the summer months when psoralens are in greatest numbers.[4] It is also common in beachgoers, florists, agricultural workers, and gardeners, all of which have both exposure to plants and sunlight.[5]

In the acute phase of phytophotodermatitis, an oxygen-dependent cutaneous injury occurs. The injury involves psoralens on the skin surface coming into contact with ultraviolet-A radiation initiating keratinocyte apoptosis. This leads to edema and desquamation of the epidermis.[1,6] An oxygen-independent reaction occurs as ultraviolet-A radiation induces covalent binding between these plant light-activating chemicals and the DNA of skin cells.[2,7] Approximately 12 to 36 hours after exposure to the light activating chemicals in the plants, erythema with or without blisters will appear on the skin. A burning sensation to the affected area may be present. Patients may also note edema, pain, or pruritus.[8] The skin manifestations are highly variable and have been reported in some patients to mimic a partial thickness burn.[2] The reaction peaks in intensity at 48 to 72 hours after initial exposure.[4,7] A post-inflammatory hyperpigmentation remains as the healing process begins and can persist for months. The pattern of dermatitis gives important clues to the diagnosis, often appearing in a "drip mark" configuration or in an unusual sunburn pattern such as a handprint.[4]

The most common location for phytophotodermatitis is the dorsum of the hand, as it is a body surface with both psoralen contact and sun exposure. The cutaneous upper lip is a less commonly affected area but may occur secondary to biting into a psoralen-containing fruit or drinking fruit juice.[9]

The diagnosis of phytophotodermatitis is clinical and relies heavily on a thorough history and a high index of suspicion from the provider. It can be difficult to diagnose because it is often mistaken for atopic dermatitis, chemical burns, melasma, or even child abuse.[7,9] Management of the dermatitis depends on the area of skin involvement as well as the intensity. In mild cases, the treatment is conservative, symptomatic care with cool moist dressings. If the dermatitis is severe, involving more than 30% of total body surface area, patient transfer to a burn care center is indicated. Topical corticosteroids may be used to help diminish patient discomfort and minimize post-inflammatory hyperpigmentation. Oral corticosteroids are rarely indicated, but may be helpful to control inflammation for patients with very severe cases.[7] Making the diagnosis is important for patient education and prevention measures. An early diagnosis allows for early initiation of topical corticosteroid therapy to diminish the degree of hyperpigmentation which may be a cosmetic concern for affected individuals.[5] Sunscreens containing physical blockers of ultraviolet-A radiation such as zinc oxide and titanium dioxide are recommended to prevent further epithelial damage and inflammation. Bleaching agents such as hydroquinone are rarely indicated as the hyperpigmentation will fade over the several-month healing process.[10]

In summary, phytophotodermatitis is a phototoxic skin reaction to cutaneous contact with psoralens in plants and plant extracts, such as lime or lemon juice, and subsequent exposure to ultraviolet-A sunlight. The patient may present with an unusual distribution pattern, as our patient did with sunburn-like drip marks down his trunk. It is a clinical diagnosis requiring a high index of suspicion by the provider. Depending on the extent of cutaneous damage, management of phytophotodermatitis may involve conservative care with cooling agents and topical corticosteroids or, in extreme cases, may require admission to a burn center. Our patient was treated conservatively because of his mild asymptomatic clinical presentation. Daily sunscreen application was strongly encouraged to minimize additional epithelial damage from ultraviolet light exposure in the following weeks. High-potency topical corticosteroids were not included in the treatment plan of this case due to the patient's asymptomatic presentation and lack of cosmetic concern regarding potential post-inflammatory hyperpigmentation. Patient education is important with this skin condition as prevention measures may considerably reduce the likelihood of a subsequent episode. Referral to a dermatologist or burn center is only indicated in severe cases.

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Calendar of Events

September 18-20, 2015

OPSO Annual Primary Care CME
Downtown Portland Embassy Suites
Portland, Oregon
www.opso.org

October 17-21, 2015

OMED 2015: ACOFP/AOA's 121st Annual Osteopathic Medical Conference & Exhibition
Hyatt Hilton and Convention Center
Orlando, Florida
www.acofp.org

November 5-8, 2015

WVOMA 113th Annual Fall CME Conference
The Greenbrier Resort
White Sulphur Springs, West Virginia
www.wvoma.org

December 3, 2015

IOA 34th Annual Winter Update
Sheraton Hotel at Keystone Crossing
Indianapolis, Indiana
www.inosteo.org

January 13-16, 2016

27th Annual Osteopathic Winter Seminar
Sand Pearl Hotel
Clearwater Beach, Florida
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JULY/AUGUST 2015 ANSWERS: **1.** D **2.** D **3.** D **4.** C **5.** A **6.** B **7.** A **8.** D **9.** D **10.** A

OFP Patient Education Handout

Peter Zajac, DO, FACOFP, Author • Amy J. Keenum, DO, PharmD, Editor
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SEX COUNSELING

Many men and women have at least one problem related to sex. The frequency of these problems can increase with age. Couples feel more open to talk to a doctor about sexual problems because of the greater level of openness in society with regard to sexual issues. Effective sex counseling for couples relies on providing a supportive, comfortable, open and confident educational environment. The couple can discuss their difficulties and the most appropriate course of action that will work best for their relationship.

Factors Related to Sexual Dysfunction:

- Physical illness in either partner. Common physical causes of sexual desire issues include endocrine and heart related medical conditions and medications such as antidepressants.
- Mental health problems in either partner such as anxiety and depression.
- Common related psychosocial issues include: religious beliefs or values; prior dysfunctional relationships; unwanted sexual experiences; and current relationship issues such as fear of commitment or separation; having children; role equity; drifting apart; adaptation to life events; and affairs.
- Lovemaking concerns such as lack of sexual intimacy, desire, arousal or performance.
- Sexual fears or anxiety and dissatisfaction.
- Sexual pain disorders, premature ejaculation, difficulty experiencing an orgasm, confusion about gender identity or sexual orientation, and issues around sexual compulsivity or addiction.
- Relationship stress or family problems.
- Job or financial stress.

Questions?

If you have any questions about sex counseling please contact your osteopathic family doctor. Your family doctor may be able to provide assistance or work along with a therapist who specializes in sex counseling to develop a management plan best suited for you and your partner.

Source(s): Everyday Health Media, Patient info., Sex Counseling for Couples.gov, and Web MD.

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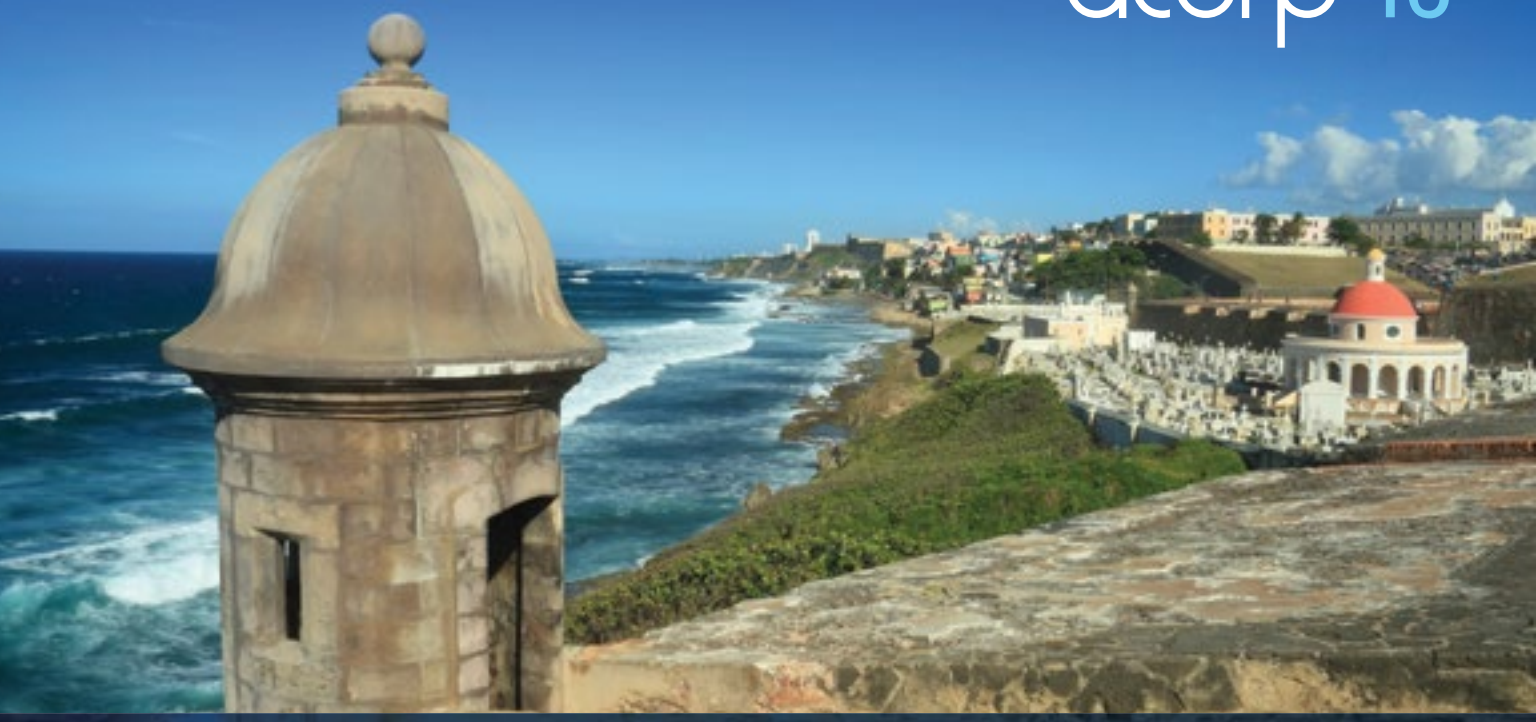

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